Novel Reactivity in Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents

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Novel Reactivity in Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents

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List of Abbreviations

AA	allylic alkylation
AAA	asymmetric allylic alkylation
Ac	acetyl
ACA	asymmetric conjugate addition
ACR	asymmetric conjugate reduction
AIBN	azobis(isobutyronitrile)
APT	attached proton test
aq	aqueous
Ar	aryl
B^-	base
BARF	sodium tetrakis(3,5-bis(trifluoro methyl)phenyl)borate
9-BBn	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert* butylcarbonyl
br	broad
*n*Bu	butyl
*i*Bu	*iso* butyl
*t*Bu	*tert* butyl
C-C bond	carbon-carbon bond
CA	conjugate addition
Cb	carbamate
Cl_2BQ	2,6-dichloro benzoquinone
CM	cross metathesis
*m*CPBA	*meta* chloroperoxy benzoic acid
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexyl carbodiimide
$(DHQ)_2AQN$	hydroquinine (anthra quinone-1,4-diyl) diether
$(DHQ)_2Phal$	hydroquinine 1,4-phthal azinediyl diether
$(DHQ)_2Pyr$	hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL-H	di *iso* butylaluminium hydride
DME	dimethoxyethane
DTBM	di *meta tert* butyl *para* methoxy
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EDC	1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide
ee	enantiomeric excess
en	enantiomer of
equiv	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
FG	functional group
G	Grubbs ligand
GC	gas chromatography
GDP	guanosine diphosphate
GTP	guanosine triphosphate
h	hour(s)
h-AAA	*hetero*-asymmetric allylic alkylation
HG	Hoveyda-Grubbs ligand
HPLC	high-pressure liquid chromatography
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
i.e.	id est (that is)
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
Im	imidazol
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
K_i	dissociation constant
L	ligand
LD50	median lethal dose
LDA	lithium di *iso* propylamide
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
LICKOR	alkyllithium-potassium alkoxide
m	multiplet
m	*meta*
M	metal
M	mol/l
MAO	methylaluminoxane
Me	methyl
Mes	mesityl
Ms	methanesulfonyl
min	minute(s)
MIRC	Michael addition-initiated ring-closure reaction
MS	mass spectrometry
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NHC	N-heterocyclic carbene

NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
*o*DPPB	*ortho* diphenyl phosphanyl benzoate
p	*para*
P	protective group
Ph	phenyl
Piv	pivaloyl
PMB	*para* methoxybenzyl
PM3	parameterized model number 3
PMHS	polymethylhydroxysiloxane
*n*Pr	propyl
*i*Pr	*iso* propyl
pyr	pyridine
q	quartet
R	alkyl
red	reductant
rt	room temperature
s	singlet
S	solvent
S_N2	bimolecular nucleophilic substitution
S_N2'	bimolecular nucleophilic allylic substitution
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert* butyldimethylsilyl
TBDPS	*tert* butyldiphenylsilyl
TC	thiophene-2-carboxylate
TEMPO	2,2,6,6-tetramethyl piperidine-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl
*p*Tol	*para* toluene
Ts	*para* toluenesulfonyl
X	halide

Chapter 1

Enantioselective Carbon-Carbon Bond Formation via Asymmetric Catalysis

Carbon-carbon bonds are the backbone of life on earth. Nature has devised several methods to construct carbon-carbon bonds in an asymmetric fashion. To interact with (the chiral receptors in) nature compounds incorporating stereogenic carbon centers are required to be synthesized. For example for pharmaceutical applications carbon-carbon bonds are regularly needed to be constructed in an enantioselective way. This chapter introduces asymmetric catalysis and, in particular, copper-catalyzed asymmetric conjugate addition of, and asymmetric allylic alkylation using Grignard reagents.

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1.1 Research towards new asymmetric synthetic methods

C-C single bonds are on average the second most thermodynamically stable homoleptic bonds (Table 1.1).[1] Furthermore, the property of carbon atoms to form four bonds to other elements allows a large number of possible carbon centers and thus a large structural diversity. Finally, the inherent electronegativity[2] of the carbon atom allows easy functionalization (Table 1.1). Either as electrophile, for instance, when a carbon atom is attached to a more electronegative oxygen atom (Figure 1.1, left), or as nucleophile, for example, when the carbon atom is part of a C-C double bond (Figure 1.1, right). Mainly due to these properties C-C bonds are the backbone of life on earth.[3]

Nature extensively uses both the electro- and nucleophilicity of carbon atoms to prepare an enormous variety of complex natural products.[4] For chemists, just marveling at these wonders of "natural synthesis" is unsatisfactory. We would like to understand on the atomic (and valence electron) level how exactly these wonders of nature are formed. Furthermore, we would like to imitate the way nature prepares these compounds omitting the immensely complex machinery, mainly consisting of specific enzymes with a molecular weight of thousand times a single carbon atom, nature has developed for their synthesis.[5] Finally, we would like to improve on nature by building complex structures using methods which nature can not develop. This chemical machinery consists of, among others, toxic metals which would cause the immediate death of living organisms at low doses.[6] This allows us to access building blocks far beyond the limited, evolutionary dictated, set of molecules nature uses.

Table 1.1. *Properties of several elements.*

element	atomic number	potential number of bonds	electronegativity	average bond energy of homoleptic single bond
H	1	1	2.1	104 kcal/mol
C	6	4	2.5	83 kcal/mol
N	7	3	3.0	39 kcal/mol
O	8	2	3.5	35 kcal/mol
F	9	1	4.0	38 kcal/mol
Cl	17	1	3.0	58 kcal/mol

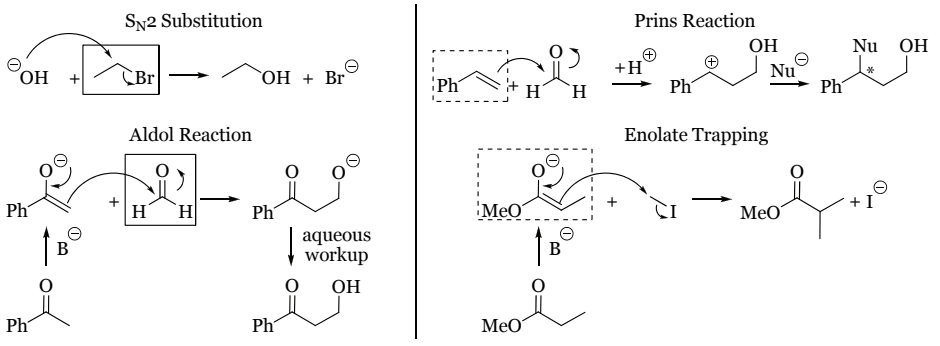
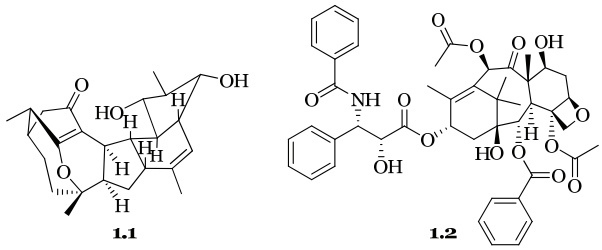


Figure 1.1. *Carbon atoms as electrophile (left, in box) or as nucleophile (right, in dotted box).*
Used abbreviations; B^-=base; Nu=nucleophile.



1.1 **1.2**

Figure 1.2. *Cyclostreptin (***1.1***, also named WS9885B or FR182877) and paclitaxel (***1.2***, also named taxol).*

Why is this interesting for non-(organic) chemists? First of all, we gain more insight in life; allowing us to manipulate nature to our benefit.[7] Secondly, chemistry allows us to manufacture complex molecules. Examples of these compounds are drugs,[8] flavors and fragrances[9] (supplements to an immense amount of daily products), insect- and herbicides[10] (together with crop improvement and fertilizers the only reason the first world can have its present level of food consumption), detergents[11] (soap) and plastics.[12] Most appealing among those products are pharmaceuticals. This is the reason why cyclostreptin[13] (**1.1**, Figure 1.2) is used to illustrate why the research towards new synthetic methodology described in this thesis has been performed.

Cyclostreptin was first discovered[13] by scientists from the Fujisawa Pharmaceutical Company and was found to be active against a variety of human cancer cell lines in low dose[13b] (IC_{50}= 21-73 x 10^{-9} g/mL, which corresponds to IC_{50}= 53-183 nM). This activity is comparable to the activity of paclitaxel (**1.2**),[14] a marketed drug against cancer. A low dose of the active ingredient of a drug is generally required to, amongst other reasons, prevent an immune response of the body, nullifying the beneficial effect of the drug, and to prevent side-effects to happen.[6] Even if a compound is active at low dose it is not guaranteed that it will be delivered in the body to the right place or that it will be free of any side-effects (by targeting other parts of the body).[6] Regularly, small changes in the chemical structure, leading to so-called analogs, are needed to obtain a molecule which can be used as a drug.[6]

So, having identified a compound with drug-like properties, the first thing researchers want to know is the exact structure of the compound. Using a variety of analytical techniques, scientists from the Fujisawa Pharmaceutical Company proposed a chemical structure for cyclostreptin.[13d] Even though the most advanced analytical methods are used, these first proposed structures are sometimes proven to be incorrect.[15] To confirm the structure of cyclostreptin, the synthetic organic research group of prof. Sorensen[16] and a variety of other groups[17] started chemical syntheses. It turned out that the predicted relative stereochemical structure was correct.[16c] However, one aspect of the structure was predicted incorrect; the absolute stereochemistry.[16c]

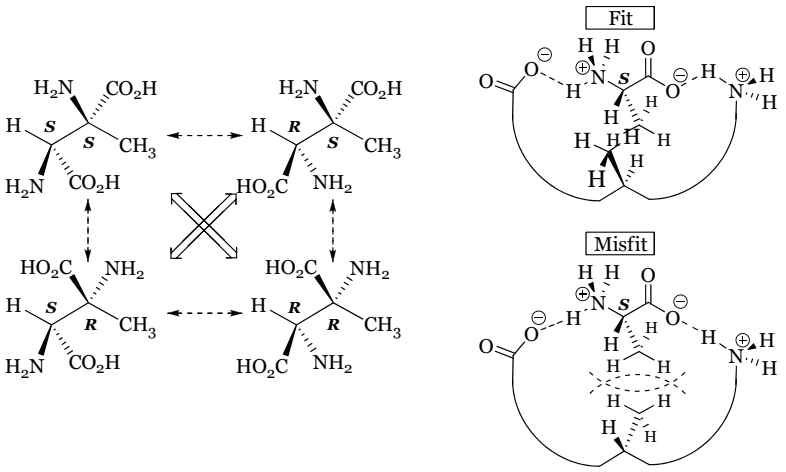


Figure 1.3. *Enantiomers (left, boxed arrows), diastereomers (left, dashed arrows) and "diastereomeric" agglomerates (right, only with the fitted structure there is sufficient interaction to form a stable complex; for the misfitted structure the interaction between the bulky methyl groups is unfavorable especially when the structures come in close proximity). R or S denotes the configuration of the stereogenic centers.*

Every molecule incorporating at least one stereogenic center (an atom surrounded with four different substituents [Figure 1.3]) and without an internal mirror plane has two mirror images. These two mirror images, the so-called enantiomers,[2] share most of their physical properties. These enantiomers can only be distinguished by derivatization with a chiral reagent and they can only be analyzed by three analytical methods. Attaching a chiral molecule to the studied molecule, so-called derivatization,[18] will give diastereomers (molecules with multiple stereogenic centers for which at least one stereogenic center has the same configuration [Figure 1.3]). Diastereomers have distinct physical properties and can be analyzed with a large number of available spectroscopic methods.[18] The only general analytical method available to distinguish and determine the absolute stereochemistry of enantiomers is X-ray diffraction.[19,20,21] Furthermore, the relative excess of one enantiomer can be analyzed by optical rotation[22] and by chiral HPLC[23] or GC.[23] The physical principle for optical rotation is the distinctive interaction of the enantiomers of (most) chiral molecules[24] with linear polarized light, giving either a positive or negative optical rotation. Chiral HPLC and GC separate the two enantiomers via their distinct interaction with a chiral stationary phase forming in situ physically different ("diastereomeric") agglomerates (Figure 1.3). Predictions of absolute stereochemistry by derivatization with another chiral molecule are most reliable, while the analytical methods currently do not have any predictive value of absolute sterochemistry.[23]

For cyclostreptin the absolute stereochemistry was originally proposed using derivatization[13d] via the Mosher ester method.[25] Using this method it was predicted that cyclostreptin was the mirror image of the compound drawn in Figure 1.2.[13d] However, when Sorensen and co-workers finished the synthesis of one stereoisomer[16c] of cyclostreptin, this molecule had the opposite sign of optical rotation and it was concluded that the enantiomer was obtained. This incorrect

prediction was confirmed by the synthesis[16d] and biological testing[26] of the other enantiomer of cyclostreptin (**1.1**). In the biological testing only **1.1** was shown to be actively interacting with the (chiral) body (in particular with microtubules, see Figure 1.4).[26]

Having identified the exact structure of cyclostreptin, its mode of action was investigated.[27] By testing synthetic **1.1**[26,27] and analogs[27] it turned out that **1.1** has a distinct mode of action compared to related anti-cancer drugs.[27b,c,28] Instead of interacting with microtubules (Figure 1.4) via hydrogen bonds or Van der Waals interactions, like other drugs targeting microtubulin formation,[29] **1.1** forms a covalent bond with microtubules, initiating the cell death of dividing cells.[27c,28] Since analogs of **1.1** lacking the conjugated C-C double bond are inactive, the compound probably reacts at this bond.[27c,28]

To summarize the preceding, following discovery of cyclostreptin[13] the structure was elucidated by organic synthesis.[16d] Via synthesis[16d] and testing[26] of both enantiomers it was proven that only (-)-cyclostreptin (**1.1**) is biologically active. Finally, using synthetic **1.1** and analogs of this compound the mode of action of **1.1** was elucidated.[27]

How does the work described in this thesis connect to the cyclostreptin story? The synthesis of **1.1** comprises of 25 chemical transformations, all discovered and developed before the first synthesis of **1.1** was completed.[16d] Synthesis of **1.1** and other complex chiral molecules will only be possible through the discovery of new reactions and of novel reactivity, and attempts to gain more mechanistic insight in chemical transformations. Furthermore, another motivation for the research towards novel methodology is to develop more efficient synthetic procedures to allow more efficient synthesis routes and, thus, decrease the manufacturing price of chemical products.

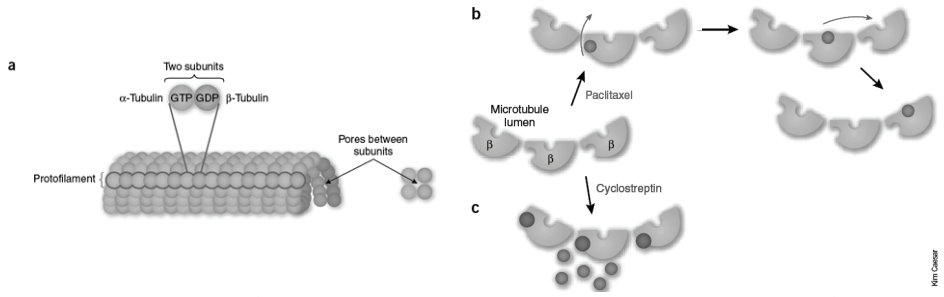


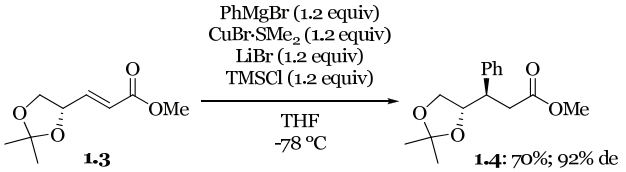
Figure 1.4. *Interaction of cyclostreptin and paclitaxel with microtubulin formation.*[28] *(a) The structure of a microtubule is thought to arise by head-to-head polymerization of tubulin dimers consisting of α and β subunits. By diffusion through the pores small molecules can enter the lumen (center). (b) Paclitaxel is proposed to bind temporarily to low-affinity sites on the exterior of the microtubule and then to migrate to the high-affinity sites within the lumen. Site exchange is believed to occur between the latter two sites. (c) Cyclostreptin binds covalently to the low-affinity site, blocking microtubule-stabilizing agents access to the lumen of the microtubule (interior). By the stabilization of the microtubules exerted by both the discussed reagents, cell division is arrested.*

Used abbreviations: GDP=guanosine diphosphate, GTP=guanosine triphosphate.

1.2 Asymmetric formation of C-C bonds

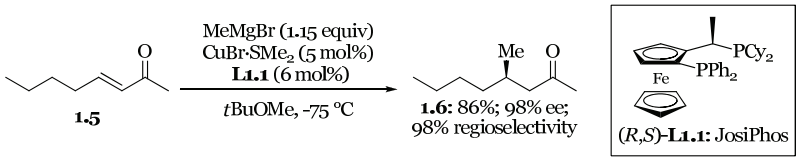
Chemists have devised a number of methods to obtain enantiomers of complex chiral molecules.[30] The simplest way to prepare a product is to start a synthesis from a chiral molecule provided by nature, from the so-called chiral pool,[31] and then to elaborate this molecule to the desired product.[31] Subsequent stereogenic centers are then formed using chiral induction of the already incorporated stereochemistry (substrate control, Scheme 1.1).[31] However, only a limited number of chiral compounds is available from the chiral pool and thus not all desired starting materials can be obtained from nature.[31] Furthermore, if a certain chiral molecule is available from the chiral pool it often only exists as a single stereoisomer.[31]

Scheme 1.1. *Chiral induction due to a stereogenic center present in the substrate.*[32]



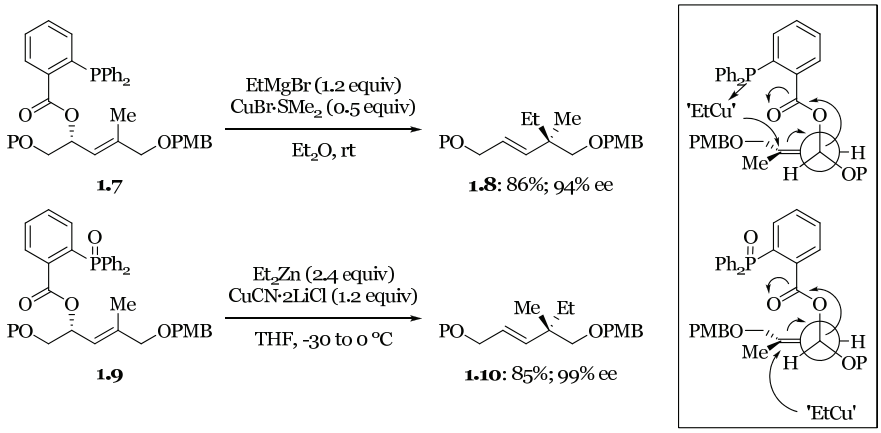
Thus, chemists have devised a number of methods to obtain enantiomerically enriched compounds starting from racemates (chiral compounds with the same amount of molecules with *R* and *S* stereochemistry). A first method is the formation of chiral agglomerates (diastereomeric salts) of one enantiomer of a compound and a chiral reagent.[23] These agglomerates can either be separated with chiral HPLC (*vide supra*)[23] or the enantiomerically enriched compound can be obtained via crystallization. A second method is the kinetic resolution of racemates;[33] chemically transforming exclusively one enantiomer to a product. A drawback of these two methodologies is that, without a racemization method for the undesired enantiomer, only 50% of yield can be obtained.[34]

Scheme 1.2. *Synthesis of a chiral molecule from a prochiral substrate.*[35]



In addition to chiral starting materials, a variety of other methods to obtain enantiomerically enriched molecules starts from prochiral substrates (molecules not yet incorporating a stereogenic center for which in a single chemical transformation a stereogenic center can be introduced, for an example see **1.5**, Scheme 1.2). First of all, chiral auxiliary groups can be attached to prochiral substrates (For example **1.7**

Scheme 1.3. *Stereoinduction by chiral auxiliaries via chelation (top) and steric repulsion (bottom) with their respective transition states (right).*[36]



Used abbreviations; P=TBDMS; PMB=*para* methoxybenzyl; 'EtCu'=cuprate reagent formed from the Cu-source and the organometallic reagent.

and **1.9**, Scheme 1.3). Then, an achiral reagent can be reacted with the substrate, forming the desired stereocenter. Finally, the chiral auxiliary can be disconnected to give the desired enantiomerically enriched product. This method is based on the so-called chiral auxiliary approach.[37] There are two main strategies for this kind of stereoinduction (Scheme 1.3). Either the auxiliary blocks one side of the substrate; only allowing the reagent to attack from the opposite side (Scheme 1.3, bottom).[37] Or the reagent is directed by a coordinating group, so-called chelation, to one side of the substrate (Scheme 1.3, top).[37]

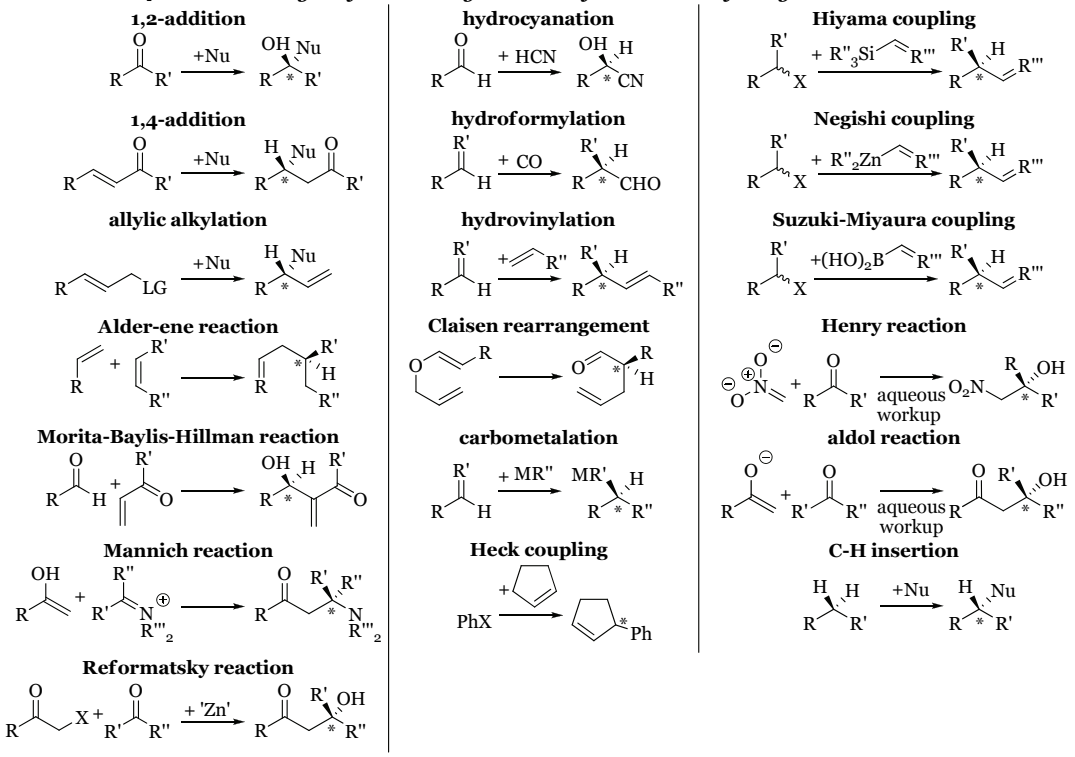
Secondly, chiral reagents can be used to attack a prochiral substrate, transferring their chirality to the substrate.[38] Finally, asymmetric catalysis (Scheme 1.2) can be used to obtain enantiomerically enriched compounds from prochiral substrates.[39]

1.3 Catalytic asymmetric formation of C-C bonds

A compound which is used in small amount (typically 5 mol% or lower) to increase the rate of a chemical transformation, ideally making a reaction more selective, without being transformed is called a catalyst. An asymmetric catalyst transfers its chirality to a superior number of prochiral substrate molecules.[39]

A number of classes of catalysts are known. First of all, chiral enzymes, either native or genetically engineered, can be used to synthesize enantiomerically enriched compounds.[40] However, the substrate scope of most enzymes is quite small.[40] A second class of catalysts consists of chiral organic molecules, the so-called organocatalysts.[41] The final class of catalysts comprises chiral metal complexes.[39] The metal catalyst class consists usually of transition metals with chiral ligands.[39]

Scheme 1.4. *Methodologies for the asymmetric formation of single C-C bonds.*



Used abbreviations; LG=leaving group; M=metal; Nu=nucleophile; X=halide.

Several asymmetric catalytic methods were developed by chemists to form a single C-C bond with over 90% ee for a wide range of substrates (Scheme 1.4). These methods comprise asymmetric 1,2-[42] and 1,4-additions,[43] enantioselective allylic alkylations,[43] asymmetric Alder-ene,[44] Morita-Baylis-Hillman,[45] Mannich[46] and Reformatsky reactions,[47] enantioselective hydrocyanations,[48] -formylations[49] and -vinylations,[50] asymmetric Claisen rearrangements,[51] enantioselective carbometalation of olefins,[52] asymmetric Heck,[53] Hiyama,[54] Negishi[54] and Suzuki-Miyaura couplings,[54] enantioselective Henry reactions,[55] the related aldol reactions[56] and finally asymmetric C-H insertions.[57]

Only a few of the asymmetric C-C bond forming methodologies can directly introduce unfunctionalized alkanes and, in particular, can introduce the highly warranted methyl group.[58]

1.4 Organometallic reagents

Due to the low electronegativity of carbon, compared to hydrogen, oxygen and nitrogen, carbon is most often encountered as an electrophile. To act as a nucleophile, carbon can be attached, for example, to elements with lower electronegativity. Attachment of carbon to zinc,[59] aluminium,[60] magnesium[61] and

lithium[62] provides nucleophilic carbon atoms. The use of these reagents, the so-called organometallic reagents is currently the most prominent way to form C-C bonds.

Organometallic reagents are most often prepared from alkyl halides by either oxidative insertion in the carbon-halogen bond[63] or metal-halogen exchange.[64] This phenomenon, changing the bond polarity to the carbon atom, is referred to as "umpolung". An alternative method to prepare an organometallic reagent is via transmetalation of an organometallic reagent with a metal with higher electronegativity.[65] Finally, organometallic reagents can be prepared by deprotonation of specific alkenyls, alkynyls and aryls.[66]

Metals with low electronegativity yield the more reactive organometallic reagents (Table 1.2). Furthermore, the reactivity of organometallic reagents depends on several factors,[67] including solvent, concentration and temperature. For zinc-, aluminium-, magnesium-, and lithium-reagents in general only a single alkyl group of an organometallic reagent can be used synthetically, the other alkyl groups are lost as unreactive species.[68] Instead organometallic reagents incorporating several alkyl groups, monoalkyl organometallic reagents, either with a halogen or a "dummy ligand",[68] can be used. In addition to a better overall atom efficiency using these monoalkyl organometallic reagents, the reactivity of the organometallic reagent can be tuned by exchanging the alkyl functionality for other functional groups.[69] Finally, among the organometallic reagents MeMgBr and MeLi are most cost-effective[70] (Table 1.2), which is important from an industrial perspective.

Table 1.2. *Electronegativity and price of several organometallic reagents.*

reagent	electronegativity metal	price
Me_2Zn	1.7	1632 €/mol
Me_3Al	1.6	158 €/mol
MeMgBr	1.3	127 €/mol
MeLi	1.0	122 €/mol

1.5 Grignard reagents

Organomagnesium or Grignard reagents were first prepared by V. Grignard in 1900.[71] Nowadays, due to the ease of preparation, their reactivity and non-toxicity, they are one of the cornerstones of chemical synthesis.[61] Grignard reagents are normally prepared from alkyl halides by oxidative insertion of magnesium powder. A whole range of alkyl (linear or branched), alkenyl, alkynyl as well as aryl Grignard reagents can be prepared.[72] Grignard reagents exhibit a limited functional group tolerance, being reactive towards, for example, carbonyls and carboxylates at room temperature. However, by handling the Grignard reagents at low temperatures they are compatible with a larger number of functionalities in substrates.[73] Furthermore, functionalized Grignard reagents can be prepared by metal-halogen exchange.[64b,74]

Among many factors, the reactivity of Grignard reagents is mainly depending on the alkyl or aryl group to be transferred,[75] the solvent, the non-transferred group,

Table 1.3. *Bond strength of RMgBr reagents in Et_2O. Determined by calorimetry of the reaction of the corresponding Grignard reagent with HBr.*

R	bond strength	R	bond strength
vinyl	69 kcal/mol	pentyl	50 kcal/mol
phenyl	69 kcal/mol	Et	49 kcal/mol
Me	60 kcal/mol	allyl	48 kcal/mol
neopentyl	54 kcal/mol	cyclopentyl	47 kcal/mol
*i*Bu	51 kcal/mol	*i*Pr	44 kcal/mol
*n*Bu	51 kcal/mol	*t*Bu	42 kcal/mol
*n*Pr	50 kcal/mol		

and the level of aggregation at a specific concentration. As derived from investigations of the bond strength of the carbon-magnesium bond in Et_2O by Holm[75] the most reactive Grignard reagents are tertiary and secondary alkyl Grignard reagents, followed by linear alkyl Grignard reagents (Table 1.3). Noteworthy is the lower reactivity of MeMgBr compared to other alkyl Grignard reagents. Finally, Grignard reagents with an sp^2 hybridization of the C-atom attached to Mg possess a lower reactivity.

Concerning the structure of the organomagnesium compounds it was discovered[76] in 1929 that in solution the monoalkylmagnesiumhalide species is in equilibrium with a dialkylmagnesium and a dihalidemagnesium species (Figure 1.5). This equilibrium was named the Schlenk equilibrium.[76,77] In Et_2O mainly the monoalkylmagnesium species is present, while, in the more Lewis basic THF the dialkylmagnesium species is most prominent in solution.[76,78] However, the equation depicted in Figure 1.5 is an oversimplification of the constitution of a Grignard reagent in solution.[76] At high concentration, for instance in Et_2O, Grignard reagents tend to aggregate.[79] The level of aggregation is dependent on a large number of factors,[79] like Lewis basicity and the properties of the solvent, the organic substituents on the magnesium atom and the size and electronegativity of the halogen atom in monoalkylmagnesium halide.

$$2\ MeMgBr \rightleftharpoons Me_2Mg + MgBr_2$$

Figure 1.5. *The Schlenk equilibrium.*
Note that possible aggregation of the depicted species is not taken into account.

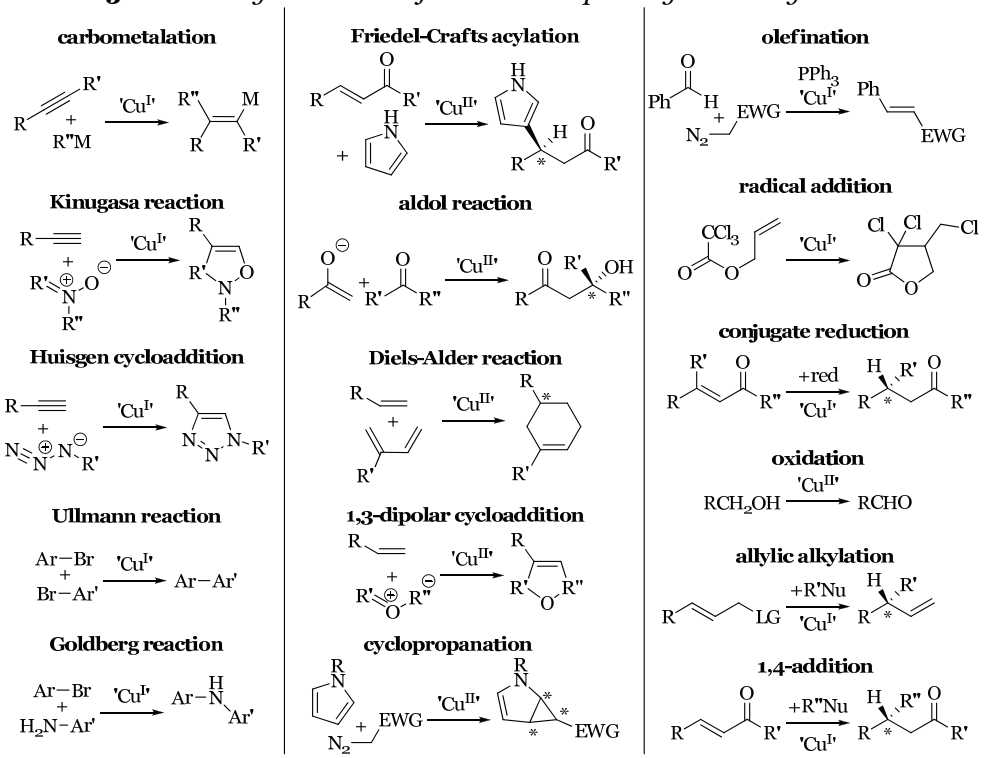
The Schlenk equilibrium in solution[80] has been studied extensively[81] by NMR,[82,83] calorimetry,[75,84] ebulliospectrometry[84a,85] and by IR and Raman spectroscopy.[86] However, some aspects of the Schlenk equilibrium require further research. First of all, the dependency of the Schlenk equilibrium on temperature has never been studied thoroughly. NMR spectroscopy has proven to be inefficient for temperature studies since the signals for dialkylmagnesium and monoalkylmagnesiumhalide coalesce at low temperatures (depending on the alkyl group of the Grignard reagent between −80 and −40 °C). For these studies IR and Raman might be better suited. Furthermore, most investigations have been devoted to the solvents Et_2O and THF while current catalysis (*vide infra*) uses mainly CH_2Cl_2, *t*BuOMe and 2-MeTHF. Finally, the influence of additives (for example copper-reagents) on the Schlenk equilibrium has never been investigated and should be examined to get a better insight in reactions employing Grignard reagents.

1.6 Copper as catalyst

Copper has a special place in the periodic system of elements.[87] With 1.9, copper has the highest electronegativity of the transition metals. Compared to the five 3d orbitals of Zn^{II} (energy levels calculated for Me_2Zn between −12.95 and −13.03 eV), the transition metal with second highest electronegativity, the five 3d orbitals of Cu^{I} are high in energy (energy levels calculated for MeCu between −6.70 and −6.86 eV).[88] Copper has five different oxidation states, Cu^{0}, Cu^{I}, Cu^{II}, Cu^{III} and Cu^{IV},[89] from which Cu^{I}, Cu^{II}, Cu^{III} are most accessible. In chemistry with organometallic reagents the Cu^{I} and the long debated Cu^{III} species[90] are mainly used. The geometry of the organometallic cuprates of the Cu^{I} oxidation state is most often linear, trigonal or distorted T-shaped.[89] The observed organometallic Cu^{III} species have been assigned a square planar geometry.[90]

The different oxidation states of copper allow Cu-chemistry to proceed via either an oxidative addition-reductive elimination mechanism[87] or a one electron oxidation or reduction mechanism.[91] Because of its high electronegativity copper is especially suited for interaction with organometallic reagents.[87,92] Organometallics with either a lower electronegativity of the metal or a similar electronegativity and a weaker carbon-metal bond can be transmetalated to copper reagents.[93] Furthermore, the reactivity of organocopper reagents is well suitable for synthetic

Scheme 1.5. *Selected synthetic transformations exploiting Cu-catalysis.*



Used abbreviations; Ar=aromatic group; LG=leaving group; M=metal; Nu=nucleophile; red=reductant.

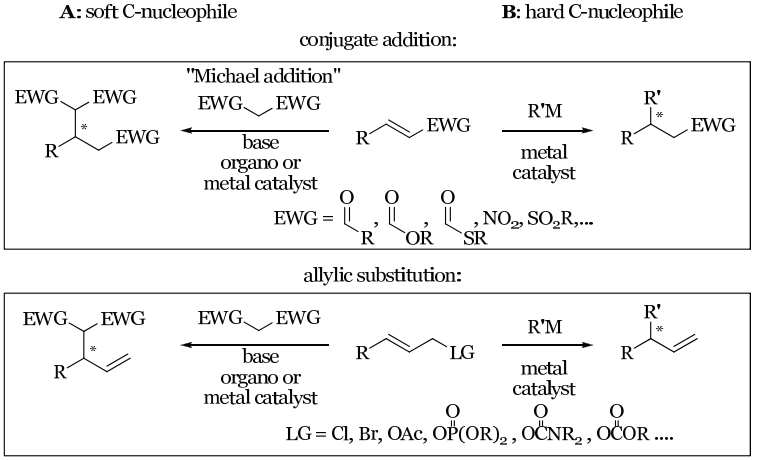
applications.[94] Compared to its neighboring elements, organometallic reagents consisting of Ni^0 or Ag^I are less stable and the organoAu^I reagents are less reactive.[87]

Copper is used in a wide variety of synthetic transformations (Scheme 1.5, previous page). The reactivity of copper towards triple bonds is exploited in carbometalations,[94] the Kinugasa reaction[95] and the Cu-catalyzed Huisgen cycloaddition, the so-called click chemistry.[96] The formal insertion of copper in aryl-halogen bonds is used for cross couplings,[97] for instance in the Ullmann[98,99] and Goldberg[99] reactions. Cu-catalysts are employed as templating Lewis acid catalysts in for example Friedel Crafts alkylations,[100] aldol reactions,[101] and cycloadditions, like the Diels-Alder[102] reaction and 1,3-dipolar cycloadditions.[103] Cu-insertion in diazocompounds[104] is exploited in cyclopropanation[104] and olefination[105] reactions. The radical chemistry of copper[106] is employed in radical additions and polymerization. Furthermore, copper reagents can be used either as reductant[107] or oxidant.[108] Finally, combined with organometallic reagents, copper reagents are used in allylic alkylations[109] and conjugate additions.[43]

1.7 Cu-catalyzed formation of C-C bonds by organometallic reagents

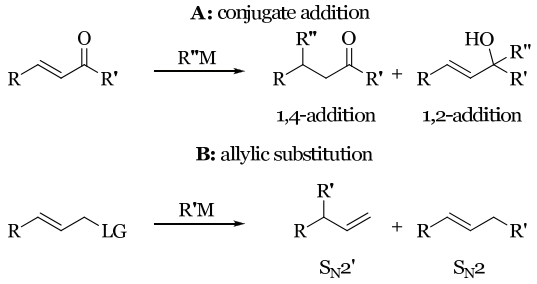
Amongst the methodologies for catalytic asymmetric synthesis described in paragraph 1.3, the conjugate addition (CA) and allylic alkylation (AA) with organometallic reagents are especially versatile for asymmetric C-C bond formation.[92,110] These transformations are complementary to the catalytic asymmetric allylic alkylation (AAA)[111,112,113] and Michael addition,[113,114] both based on soft C-nucleophiles (Scheme 1.6A). For both CA and AA, the organic moiety of the organometallic reagent reacts with the sp^2 carbon of an electron deficient substrate converting it to an sp^3 carbon (Scheme 1.6B). In the case of CA, subsequent quenching of the enolate leads to the final product, whereas for the related AA an appropriate leaving group is expelled to form the enantiomerically

Scheme 1.6. *AA and CA of soft and hard C-nucleophiles.*



Used abbreviations; EWG=electron withdrawing group; LG=leaving group; M=metal.

Scheme 1.7. *Typical competing reactions for CA (A) and AA (B).*



enriched olefin product. The organometallic compounds used most frequently for these transformations are organozinc, Grignard, organoaluminium, organolithium and cuprate reagents.[43,109,112,115,116,117]

Over the last three decades considerable effort has been directed towards the development of efficient catalytic systems for the asymmetric CA and AA reactions using organometallic reagents. Complexes derived from Cu salts and chiral ligands have provided the broadest scope in the catalyzed enantioselective CA and AA of organometallic reagents. Organozinc reagents have been the most successful of the organometallic reagents in this respect.[43a,109,115,116,117]

However, organomagnesium compounds were among the first organometallic compounds[118] to be applied to synthetic organic chemistry and the use of Grignard reagents in Cu-catalyzed CA was first reported in 1941 by Kharash and Tawney.[119] Achieving chemo-, regio- and stereocontrol in both asymmetric conjugate addition (ACA) and asymmetric allylic alkylation, however, has proven to be challenging and has restricted the application of these transformations, in particular, to total synthesis. Typical selectivity issues pertain to 1,2- versus 1,4-addition (Scheme 1.7A) and S_N2- versus S_N2'-substitution (Scheme 1.7B).

The challenge faced in the development of stereoselective C-C bond forming reactions is apparent when one considers that, despite three decades of intensive research in this area, only recently efficient Cu-catalyzed enantioselective CA of Grignard reagents has been achieved.[73] The earlier discovery of the highly enantioselective Cu-catalyzed CA of dialkylzinc reagents allowed for replacement of Grignard reagents in this asymmetric C-C bond forming reaction.[115,116,117,120] Dialkylzinc reagents offer distinct advantages over Grignard reagents in their low reactivity in non-catalyzed reactions and their high tolerance to functional groups both on the substrate and on the organozinc reagent itself.[115,120] Nevertheless, there are several advantages to the use of common mono-alkylmagnesium halide reagents, most importantly their widespread availability and the ability to transfer all of the alkyl groups of the organometallic compound. The synthetic potential of these asymmetric transformations has driven intensive research in this area and over the past few years major breakthroughs have been realized in the enantioselective CA and AA of Grignard reagents.[73,121,122]

This focus here will be on asymmetric CA and AA reactions employing Grignard reagents. Several comprehensive reviews[110,117] covering early approaches are available and hence progress in the catalyzed enantioselective CA reported since 1988 will be summarized in paragraph 1.8. Furthermore, advances in the field of enantioselective AA using Grignard reagents since 1995 will be reviewed in paragraph 1.10.

1.8 Cu-catalyzed asymmetric 1,4-addition of Grignard reagents

Asymmetric conjugate addition has received a tremendous level of attention over the past three decades. A comprehensive review on the use of organolithium and Grignard reagents using stoichiometric chiral ligands or employing chiral auxiliaries, reagents and/or substrates was published in 1992 by Rossiter and Swingle.[117] Despite the extensive application of ACA reactions in synthesis one drawback of these approaches is the use of stoichiometric amounts of chiral auxiliaries.

Enantioselective, and in particular catalyzed asymmetric, 1,4-addition of organometallic reagents presented a major challenge primarily for two reasons. First, although appreciable enantiomeric excess could be obtained with a wide variety of chiral catalysts the stereocontrol reached remained too low to see general application in synthetic chemistry. Secondly, the catalyzed enantioselective reaction must compete with the non-catalyzed addition of the highly reactive organomagnesium or organolithium reagents to either a carbonyl group (i.e. 1,2-addition, Scheme 1.7A) or to a conjugated alkene, providing a racemic 1,4-addition product.

1.8.1 Early studies on catalyzed ACA

The first example of a catalyzed ACA of Grignard reagents was reported by Lippard and co-workers in 1988.[123] In this seminal contribution the authors demonstrate the possibility of asymmetric induction in the CA of Grignard reagents using catalytic amounts of a chiral ligand. Improvements to the regio- (1,4- vs. 1,2-addition) and enantioselectivity (up to 14%) were obtained for the CA of *n*BuMgBr to cyclohexenone using 2 to 4 mol% of catalyst. The chiral catalyst was based on chiral bidentate *N*,*N*'-dialkyl substituted aminotroponeimine ligands depicted in Scheme 1.8 (**L1.2** and **L1.3**) with CuBr•SMe_2 as the metal source and PhLi or *n*BuLi to form the active complex.

Scheme 1.8. *First examples of asymmetric induction in catalytic CA of Grignard reagents.*

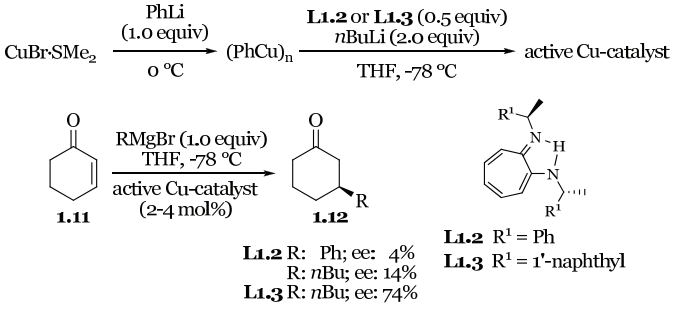
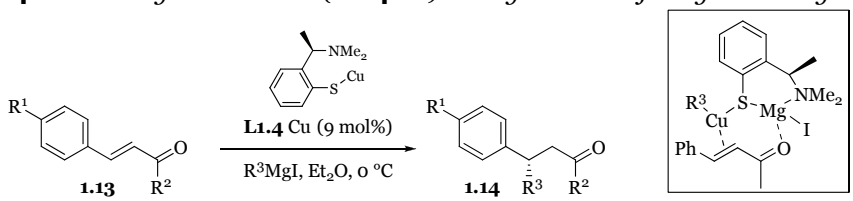


Table 1.4. *Chiral aryl-thiolate Cu (***L1.4** *Cu) catalyzed ACA of Grignard reagents.*



entry	R¹	R²	R³	ee (%)
1	H	Me	Me	76
2	H	*i*Pr	Me	72
3	Cl	Me	Me	69
4	CN	Me	Me	13
5	OMe	Me	Me	56
6	H	*t*Bu	Me	45
7	H	Ph	Me	0
8	H	Me	*n*Bu	45
9	H	Me	*i*Pr	10

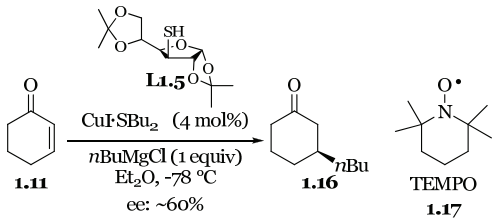
Although the selectivity was low initially, additives were soon found by Lippard and co-workers,[123a] that allowed for a significant improvement in enantioselectivity up to 70%. Most notable, HMPA and Si-reagents accelerated the CA of organocuprates and provided an improvement in enantioselectivity.[123b]

In 1991 van Koten and co-workers introduced the chiral bidentate aryl-thiolate ligated Cu complex (**L1.4** Cu) as a catalyst for the CA of Grignard reagents (Table 1.4).[124] It was shown that high regio- and modest enantioselectivity could be obtained in the CA of MeMgI to benzylideneacetone using 9 mol% of the arenethiolato Cu^{I} complex **L1.4** Cu (entries 1-3). However, the reaction proved to be sensitive to the reaction conditions[125] including changes in solvent and substrate. Furthermore, in order to achieve the highest level of regio- and enantioselectivity both Grignard reagent and enone were added together in a continuous manner to the catalyst.

The use of THF rather than Et_2O resulted in a complete lack of enantioselectivity. Similarly, the use of Grignard reagents other than MeMgI or the use of other substrates resulted in lower enantioselectivity (entries 4-9). In contrast with the results obtained by Lippard and co-workers,[123b] the use of additives such as silyl-compounds and HMPA resulted in a decrease in both regio- and enantioselectivity.

However, the enantioselectivity of the CA of MeMgI to benzylideneacetone was improved by the use of toluene as solvent. In addition, the reaction proceeded with only 3 mol% of catalyst **L1.4** Cu.[124d] Model studies indicated that $[CuSAr\text{-}(R)\text{-}CHCH_3NMe_2]_3$ reacts with R^3MgI to form the aggregate $[CuR^3]_4[Mg(SAr\text{-}(R)\text{-}CHCH_3NMe_2)_2]_2$. It was proposed that from this aggregate intermediate **1.15** is formed through interaction with the substrate. The enone binds the dinuclear Cu-Mg arenethiolate unit with the olefinic bond coordinating to copper and the carbonyl oxygen binding to magnesium. From this complex the alkyl moiety of the Grignard reagent is transferred to the β-position of the enone.

Scheme 1.9. *Cu-catalyzed ACA of Grignard reagents using the thioglucofuranose ligand* **L1.5**.

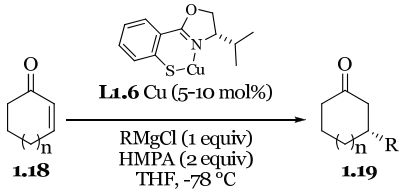


Another chiral thiol-based catalyst was reported by Spescha and Rihs[126] in 1991 for the CA of RMgX (R = *n*Bu, Ph) to several α,β-unsaturated carbonyl compounds. This catalyst was prepared *in situ* from chiral thioglucofuranose **L1.5**, CuI•SBu_2 and *n*BuLi (Scheme 1.9). The highest ee (60%) was obtained for the CA of *n*BuMgBr to cyclohexenone using 4 mol% catalyst loading in Et_2O at −78 °C.

The reproducibility of the enantioselectivity in this ACA was improved by the presence of TEMPO, which is proposed to react with excess *n*BuLi that was used for preparation of the catalyst. *n*BuLi can engage in the direct 1,4-CA or 1,2-addition to the substrate leading to racemic products. A decrease in both the regio- and enantioselectivity was observed when *n*BuMgCl was replaced by nBu_2Mg or when THF was used as solvent in place of Et_2O. These effects are most likely due to changes in the Schlenk equilibrium resulting in the formation of other aggregated species.

An important improvement in the CA of Grignard reagents was achieved by Zhou and Pfaltz[127] with the introduction of a structural analog (i.e. **L1.6** Cu, Table 1.5) of the arenethiolate Cu(I) complex (**L1.4** Cu, Table 1.4) developed by van Koten and co-workers.[124c] The primary change in the structure of the catalyst is the more rigid chiral moiety (oxazoline vs. dimethylbenzylamine). Cu(I) thiolate complex **L1.6** Cu proved to be the most efficient catalyst for cyclic enones with the best results observed in THF in the presence of 2 equiv of HMPA at low temperature. High regioselectivity and moderate enantioselectivity was obtained in the

Table 1.5. *Thiolate complex (***L1.6** *Cu) used in the ACA of Grignard reagents to cyclic enones.*



entry	n	R	ee (%)
1	1	*n*Bu	60
2	1	*i*Pr	72
3	0	*n*Bu	16
4	0	*i*Pr	37
5	2	*n*Bu	83
6	2	*i*Pr	87

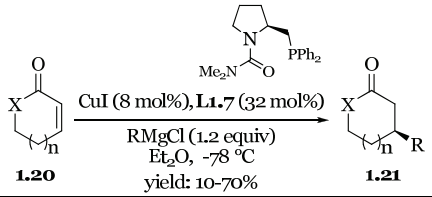
CA of the *n*Bu (entry 1) and *i*Pr (entry 2) Grignard reagents. Omitting HMPA or the use of Et_2O as solvent both resulted in a loss of enantioselectivity. Furthermore, addition of Si-derivatives did not affect the enantioselectivity.

This catalyst system allows for the ACA of *i*PrMgCl and *n*BuMgCl to several cyclic enone substrates (entries 3-6) with the highest enantioselectivity obtained for the CA of *i*PrMgCl to 2-cycloheptenone (87%, entry 6). In several cases it was necessary to increase the catalyst loading to 10 mol% to improve yields. For acyclic enones, enantioselectivity below 20% was obtained using this catalyst system.

Tomioka and co-workers have obtained high enantioselectivity (up to 92%, Table 1.6) in the CA of organocuprates formed using *n*BuMgCl in the presence of stoichiometric amounts of chiral ureaphosphine **L1.7**.[128] In a subsequent detailed study they demonstrated that a catalyst loading of 32 mol% of chiral **L1.7** and 8 mol% Cu salt in Et_2O provided optimal efficiency. With polar solvents (such as THF and Me_2S) considerably lower enantioselectivity was obtained. As mentioned before, the counter ion can have a major influence on the outcome of the Cu-catalyzed ACA of Grignard reagents. Iodide was identified as the most suitable counter ion in the catalyzed reaction while for the stoichiometric reaction cyanide was the counter ion of choice. The halide of the Grignard reagent is also critical. The highest efficiency in terms of yield, regio- and enantioselectivity was obtained using a chloride based Grignard reagent. Notably, the use of nBu_2Mg in place of *n*BuMgCl still provided high enantioselectivity (92%) albeit with lower regioselectivity.

In addition to optimization of the reaction conditions, Tomioka and co-workers[128] studied the scope of their system with respect to Grignard reagent and enones. High enantioselectivity and moderate to good yields were obtained using

Table 1.6. *Cu-catalyzed ACA of Grignard reagents using an ureaphosphine catalyst (***L1.7***).*



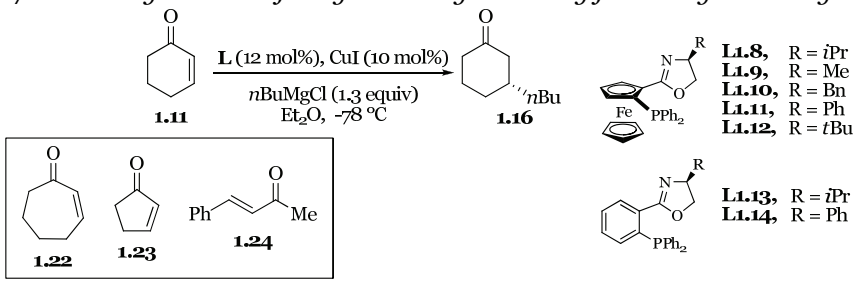
1.20 **1.21**

entry	n	X	R	ee (%)
1	1	CH_2	Et	73
2	1	CH_2	*n*Pr	72
3	1	CH_2	*n*Bu	90
4	1	CH_2	hexyl	92
5	1	CH_2	$BnCH_2$	87
6	2	CH_2	*n*Bu	81
7	1	O	*n*Bu	91
8	1	O	hexyl	90
9	0	CH_2	*n*Bu	42
10	1	CH_2	Me	5
11	1	CH_2	Ph	4
12	1	CH_2	Bn	12
13	1	CH_2	*i*Pr	4

linear Grignard reagents (Et, *n*Pr, *n*Bu, hexyl, $BnCH_2$, entries 1-5) for the CA to cycloheptenone (entry 6) and dihydropyranone (entries 7, 8). For CA to cyclopentenone moderate enantioselectivity was obtained (entry 9). Finally, MeMgCl, aryl, benzyl andbranched alkyl Grignard reagents (entries 10-13) provided much lower enantio- and regioselectivity. The lower enantio- and regioselectivity was not due to decomposition of the catalyst as the chiral phosphine ligand could be recovered and reused without loss of enantioselectivity. The mechanism and the exact nature of the chiral catalyst involved remain to be elucidated for this system. Prior to 2003, the results obtained by Tomioka and co-workers[128] represented the state of the art with regard to enantioselectivity (92%). However, a major drawback of this system is the high catalyst loading required (32 mol%).

Stangeland and Sammakia[129] achieved asymmetric induction in the Cu-catalyzed CA of Grignard reagents by combining planar chirality and a stereogenic centre in the ligand structure (Table 1.7). With 12 mol% of the chiral ligand **L1.8** and 10 mol% of CuI in Et_2O the product of the addition of *n*BuMgCl to cyclohexenone was obtained in good yield and 83% ee (entry 1). A slight reduction in enantioselectivity (74%) was observed when additives (HMPA, TMSCl or MeI) were present; whereas in THF the reaction was barely enantioselective (6% ee). Variation in the ligand structure showed that the enantioselectivity was insensitive to the size of the alkyl group in the oxazoline ring (entries 2-4) with the exception of the *t*Bu substituted oxazoline **L1.12** (entry 5). With the benzyl **L1.10** and phenyl **L1.11** oxazoline ligands, however, a substantial increase in regioselectivity (up to 10 times) was observed. In the absence of planar chirality little, if any, enantioselectivity was observed (entries 6 and 7).

Table 1.7. *Cu-catalyzed ACA of Grignard reagents using ferrocenyl based ligands.*



entry	substrate	L	yield (%)	regioselectivity (%)[a]	ee (%)
1	**1.11**	**L1.8**	80	91	83
2	**1.11**	**L1.9**	68	83	81
3	**1.11**	**L1.10**	97	>99	82
4	**1.11**	**L1.11**	97	>99	83
5	**1.11**	**L1.12**	87	99	46
6[b]	**1.11**	**L1.13**	77	98	26
7	**1.11**	**L1.14**	6	9	0
8	**1.22**	**L1.11**	82	>99	92
9	**1.23**	**L1.11**	82	>99	65
10	**1.24**	**L1.11**	61	99	81

[a] Regioselectivity: [1,4/(1,4+1,2)] x 100. [b] Enantiomer of the catalyst used and the enantiomer of the product obtained.

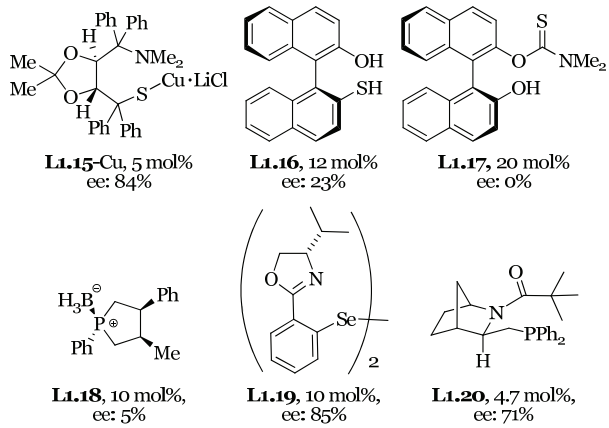


Figure 1.6. *Highest ee values obtained for the Cu-catalyzed ACA of Grignard reagents with several ligands.*
L1.15[130a]; **L1.16** and **L1.17**[130b,c]; **L1.18**[130d]; **L1.19**[130e]; **L1.20**[130f]

The scope of the ACA of Grignard reagents to enones was investigated using ligand **L1.11**. As observed with the ligand developed by Tomioka *et al.*,[128] the highest enantioselectivity (92%) was obtained for addition of *n*BuMgCl to cycloheptenone **1.22** (entry 8). For cyclopentenone **1.23** (entry 9), a lower ee of 65% was obtained, in accordance with a trend in stereoselectivity observed frequently in catalysis upon changing from a 6- to a 5-membered cyclic enone.[116,120,129] Interestingly, the use of acyclic enone **1.24** yielded similar results to those obtained for the cyclic systems (61% yield and 81% ee, entry 10).

A broad range of structurally diverse chiral ligands in combination with a copper source were tested in the CA of Grignard reagents (for example **L1.15**-**L1.20**, Figure 1.6). For these ligands good regioselectivity, albeit typically poor to modest enantioselectivity, has been obtained.[130] In particular, the aminothiol ligand (**L1.15**) by Seebach and co-workers[130a] and the diselenide oxazoline ligand (**L1.19**) by Braga and co-workers[130e] show promising levels of enantioselectivity.

1.8.2 Catalytic ACA to enones

It is apparent from the studies described above that; i) the reactivity of the Grignard reagent does not preclude Cu-catalyzed enantioselective alkyl transfer i.e. the ACA can compete with the non-catalyzed carbon-carbon bond forming reaction. ii) Appreciable levels of enantioselectivity can be reached with several, structurally diverse, chiral ligands. iii) The catalyzed ACA of Grignard reagents is frequently highly sensitive to changes in solvent, concentration, temperature and the rate of addition of reagents. iv) A pronounced substrate dependence is observed. v) Enantioselectivity, although promising in some cases, had not reached the levels required for general application in synthetic organic chemistry. vi) Several chiral and achiral Cu complexes that are active in catalyzing the ACA of Grignard reagents appear to be present under many of the catalysis conditions employed. Furthermore, for the CA reaction it was observed that non-ligated copper salts are capable of catalyzing the CA reaction of Grignard reagents to enones. Therefore, it is

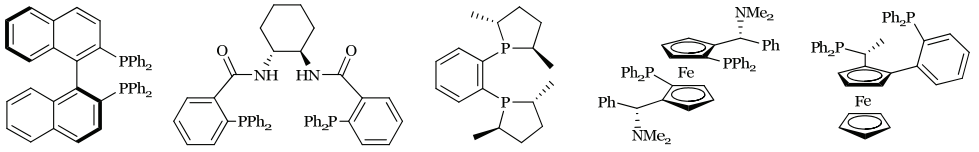
necessary that a chiral ligand coordinates strongly to the Cu^{I} ion to avoid non-stereoselective catalysis by free Cu^{I} in solution.

Although chiral diphosphine ligands (Figure 1.7) have dominated the field of asymmetric catalysis over the last 30 years,[39,110] until recently these ligands were not reported to be effective in the conjugate addition of Grignard reagents. Most of the ligands used previously in the CA of Grignard reagents incorporate a phosphor, sulfur or selenium atom in combination with a nitrogen or an oxygen donor atom to coordinate selectively with the copper and magnesium in the catalytically active complex. In principle, diphosphines do not fulfill the paradigm of the *metal-differentiating coordination concept*.[131] Indeed, as part of a screening program Feringa and co-workers[73] observed that the bidentate phosphine ligands such as BINAP (**L1.21**), Trost ligand (**L1.22**), and DuPhos (**L1.23**) provided poor enantioselectivity in the ACA of Grignard reagents (Figure 1.7).

Among the most important of the bidentate ligands in asymmetric catalysis are the ferrocenyl diphosphine ligands,[132] in particular TaniaPhos (**L1.26**, Figure 1.8)[132a,b] and JosiPhos (**L1.1**).[132c,d] In recent years, these ligands have been used especially for enantioselective hydrogenation reactions and have proven to be successful in a variety of other asymmetric transformations as well.[132e,f,g] Moreover, ferrocenyl-based ligands showed promising enantioselectivity in the Cu-catalyzed conjugate addition of dialkylzinc reagents to enones.[129,132h]

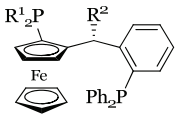
Initial results with ferrocenyl-based diphosphines[132d,133] indicated their potential for CA of Grignard reagents (45% ee with MandyPhos (**L1.24**, Figure 1.7) and 70% ee with WalPhos (**L1.25**), respectively) and formed the basis for the breakthrough in the catalyzed ACA of Grignard reagents made in 2004.[73]

It was soon established that among the ferrocenyl ligands (Figure 1.8) tested for the ACA of Grignard reagents to cyclic enones the highest enantioselectivity was obtained with the ligand TaniaPhos (**L1.26**).[73]

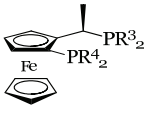


L1.21: BINAP **L1.22**: Trost Ligand **L1.23**: DuPhos **L1.24**: MandyPhos **L1.25**: WalPhos

Figure 1.7. *Chiral diphosphine ligands*



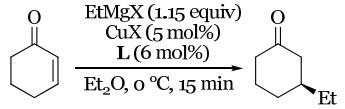
(*R,R*)-**L1.26**, R^1: Ph, R^2: NMe_2, TaniaPhos
(*R,R*)-**L1.27**, R^1: Cy, R^2: NMe_2
(*R,R*)-**L1.28**, R^1: Ph, R^2: N*n*Pr_2
(*R,R*)-**L1.29**, R^1: Ph, R^2: pyrrolidine
(*R,R*)-**L1.30**, R^1: Ph, R^2: Me



(*R,S*)-**L1.1**, R^3: Cy, R^4: Ph, JosiPhos
(*R,S*)-**L1.31**, R^3: Ph, R^4: Cy, rev. JosiPhos
(*R,S*)-**L1.32**, R^3: *t*Bu, R^4: Ph
(*R,S*)-**L1.33**, R^3: Ph, R^4: Ph
(*R,S*)-**L1.34**, R^3: xylyl, R^4: Ph
(*R,S*)-**L1.35**, R^3: Cy, R^4: Cy

Figure 1.8. *Chiral ferrocenyl ligands.*
Cy=cyclohexyl.

Table 1.8. *Cu-catalyzed ACA of Grignard reagents to cyclohexenone with ferrocenyl-based catalysts.*



1.11 **1.25**

entry	EtMgX	X	**L**	regioselectivity (%)[a]	ee (%)	*R/S*
1	EtMgCl	I	**L1.26**	43	93	*R*
2	EtMgCl	Br	**L1.26**	61	95	*R*
3	EtMgCl	Cl	**L1.26**	71	95	*R*
4	EtMgBr	Cl	**L1.26**	95	96	*R*
5	EtMgBr	Cl	**L1.27**	80	10	*R*
6	EtMgBr	Cl	**L1.28**	96	94	*R*
7	EtMgBr	Cl	**L1.29**	92	93	*R*
8	EtMgBr	Cl	**L1.30**	69	45	*R*
9	EtMgBr	Cl	**L1.1**	93	30	*S*

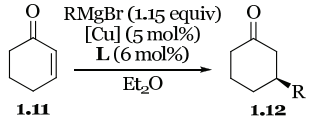
[a] Regioselectivity: [1,4/(1,4+1,2)] x 100.

With TaniaPhos (**L1.26**, Table 1.8, entries 1-3) high enantioselectivity and moderate regioselectivity were obtained in the Cu^{I}-catalyzed CA of EtMgCl to cyclohexenone. Optimization of reaction conditions for the model system depicted in Table 1.8 identified that the use of 5 mol% of CuCl and 6 mol% of **L1.26** at 0 °C in Et_2O with EtMgBr provided both excellent regio- and enantioselectivity (entry 4).

Conversion was complete in 15 min using these conditions. Furthermore, high regio- (95% 1,4-addition product) and enantioselectivity (96% ee) was obtained. Analogs of TaniaPhos (**L1.26**) were tested under these conditions to identify the key structural features of the catalyst. Replacing the phenyl groups with cyclohexyl groups (**L1.27**, entry 5) led to a large decrease in enantioselectivity. Surprisingly, variation of the amine substituent R^2 (**L1.28**, entry 6 and **L1.29**, entry 7) had little effect on the enantioselectivity. By contrast, replacement of the amine group by a methyl group (**L1.30**, entry 8) reduced the enantioselectivity as well as the regioselectivity. With the JosiPhos ligand (**L1.1**, entry 9) the opposite enantiomer was obtained with lower enantioselectivity.

The CA of a series of Grignard reagents to cyclohexenone was examined under these reaction conditions (Table 1.9, see next page). For RMgBr reagents with linear alkyl chains (R = Et, Me, *n*Pr, *n*Bu; entries 1-4) the CA products **1.12** were obtained with excellent enantioselectivity (90-96% ee). The substitution pattern was found to have a major influence on the enantioselectivity achieved. With Grignard reagents containing branched alkyl chains (in particular *i*Pr and *i*Bu Grignard reagents) CA proceeded with low enantioselectivity (entries 5, 6). *Iso* amylMgBr afforded the 1,4-addition product with 95% ee (entry 7). Grignard reagents substituted at the β- or δ-position also afforded good enantioselectivity (entries 8 and 9). With the ligand JosiPhos (**L1.1**), the CA of *i*PrMgBr and *i*BuMgBr provided excellent regiocontrol (99%) albeit with moderate to high enantioselectivity (54% and 92% ee respectively, entry 10 and 11). The JosiPhos based catalyst system shows only modest enantioselectivity for the CA of PhMgBr (entry 12).[134]

Table 1.9. Cu-catalyzed ACA of Grignard reagents to cyclohexenone.



1.11 1.12

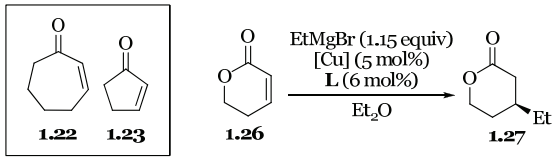
entry	R	[Cu]	L	regioselectivity (%)[a]	ee (%)
1	Et	CuCl	**L1.26**	95	96
2	Me	CuCl	**L1.26**	83	90
3	*n*Pr	CuCl	**L1.26**	81	94
4	*n*Bu	CuCl	**L1.26**	88	96
5	*i*Pr	CuCl	**L1.26**	78	1
6	*i*Bu	CuCl	**L1.26**	62	33
7	isoamyl	CuCl	**L1.26**	76	95
8	CH_2Bn	CuCl	**L1.26**	80	77
9	4-Cl-*n*Bu	CuCl	**L1.26**	79	85
10	*i*Pr	CuBr•SMe_2	**L1.1**	99	54
11	*i*Bu	CuBr•SMe_2	**L1.1**	99	92
12	Ph	CuBr•SMe_2	**L1.1**	50	40

[a] Regioselectivity: [1,4/(1,4+1,2)] x 100.

For the CA of simple alkylMgBr to other cyclic enones and unsaturated lactones the same conditions can be used to reach modest to high enantioselectivity (Table 1.10). However, the ferrocenyl diphosphine ligand that provides optimum results is dependent on the specific structure of the cyclic substrate.

Several ferrocenyl diphosphine ligands afford enantioselectivities over 70% in the Cu-catalyzed CA of Grignard reagents to cycloheptenone. TaniaPhos (**L1.26**) and JosiPhos (**L1.1**) gave the product with 87% (entry 1) and 78% ee (entry 2), respectively, albeit with opposite configurations. For cyclopentenone, the JosiPhos type ligands provided better regio- and enantioselectivity than TaniaPhos (**L1.26**,

Table 1.10. *Cu-catalyzed ACA of Grignard reagents to cyclic enones.*

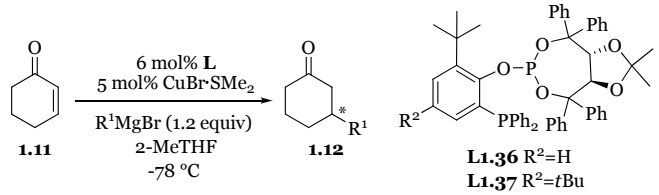


1.22 1.23 1.26 1.27

entry	substrate	L	regioselectivity (%)[a]	ee (%)	*R/S*
1	**1.22**	**L1.26**	80	87	*R*
2	**1.22**	**L1.1**	96	78	*S*
3	**1.23**	**L1.26**	69	6	*S*
4	**1.23**	**L1.1**	99	82	*R*
5	**1.23**	**L1.32**	99	92	*R*
6	**1.26**	**L1.26**	99	47	*R*
7	**1.26**	**L1.1**	99	79	*S*
8	**1.26**	**L1.32**	99	82	*S*

[a] Regioselectivity: [1,4/(1,4+1,2)] x 100.

Table 1.11. *Addition of sp²-hybridized Grignard reagents to cyclohexenone.*



entry	R^1	L	1,2:1,4	yield (%)	ee (%)	*R/S*
1	*iso* propenyl	**L1.36**	9:91	49	92	*R*
2	Ph	**L1.36**	9:91	50	92	*R*
3	Et	**L1.36**	11:89	60	90	*S*

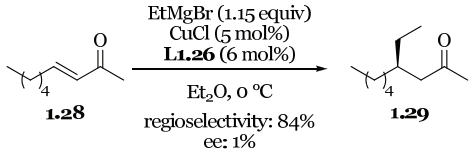
entries 4 and 5 vs. entry 3). For example, with ligand **L1.32** the 1,4-adduct could be obtained with 99% regioselectivity and 92% ee (entry 5). In accordance with the observations of Stangeland and Sammakia,[129] for the CA to cycloheptenone or cyclopentenone, respectively, a reversal of the sense of the asymmetric induction was observed. For α,β-unsaturated lactones the JosiPhos ligand (**L1.1**) and the related chiral phosphine **L1.32** provided higher enantioselectivity (79% and 82% ee, entry 6 and 7, respectively) than that obtained with TaniaPhos (**L1.26**, 47% ee, entry 8). For these cyclic substrates further improvements in the enantioselectivity of the reaction, in comparison to the selectivity obtained for cyclohexenones, still remain a challenge.

The Grignard scope of the ACA has been limited to alkyl Grignard reagents. However, in 2008 Schmalz and co-workers[135] published the use of bidentate Taddol-derived phosphine-phosphite ligands (**L1.36** and **L1.37**) in combination with CuBr•SMe_2 in ACA to cyclohexenone using 2-MeTHF as solvent. Results with respect to enantioselectivity were generally inferior to those with the Josiphos-type system. However, these ligands allow the addition of sp²-hybridized Grignard reagents in moderate yields and high enantioselectivity (Table 1.11, entry 1 and 2). Interestingly, in the addition of the sp²-hybridized compared to sp³-hybridized Grignard reagents a switch of enantiofacial selectivity was observed.

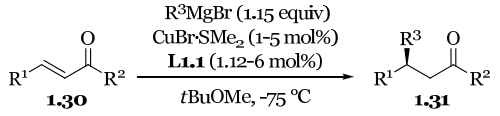
An important challenge in the field of catalyzed ACA of Grignard reagents is the expansion of the scope of the catalyst system to address acyclic α,β-unsaturated enones. Although the products of CA of organometallic reagents to acyclic enones are important subunits of biologically active molecules, there was a paucity of highly enantioselective catalyzed routes for their preparation.[116c,136] Notable exceptions are the Cu-catalyzed CA of dialkylzinc reagents[43,116] described by both Hoveyda and co-workers[137a] and by Nakamura and co-workers.[137b] A complementary approach reported by Lipshutz and co-workers and Buchwald and co-workers relies on a Cu-catalyzed asymmetric conjugate reduction of *β,β*-disubstituted enones.[132e,138] However, a general method based on the ACA of organomagnesium reagents to acyclic enones was, until recently, unavailable.[i] Initial studies were carried out using the catalyst system that showed success in the CA of EtMgBr to cyclic enones. For the linear substrate *E*-3-nonen-2-one, the combination of TaniaPhos (**L1.26**) and

[i] Promising results (ee < 82%) limited to benzylideneacetone were reported in refs 124c and 129.

Scheme 1.10. *Initial results for catalyzed ACA of Grignard reagents to acyclic enones.*



Scheme 1.11. *Cu-catalyzed ACA of Grignard reagents to acyclic enones.*



R¹: Me, *n*Pr, *n*Bu, pentyl; R²: Me, *n*Bu;
R³: Me, Et, *n*Pr, *n*Bu, *i*Bu, *iso* amyl, 4-Cl-*n*Bu
regioselectivity: 88-98%; ee: 86-98%; 21 examples

For R¹: 2-thienyl, 2-furyl; regioselectivity: 66-74%; ee: 96-97%
For R²: *t*Bu; regioselectivity: 54%; ee: 40%
For R³: *i*Pr; regioselectivity: 92%; ee: 48%
For R³: Ph; regioselectivity: 62%; ee: 76%

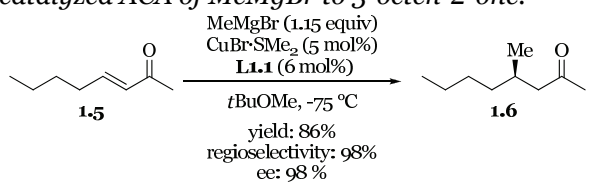
CuCl at 0 °C provided the 1,4-addition product (Scheme 1.10). However, the lack of enantioselectivity and low regioselectivity obtained demonstrates once again the strong dependence of the outcome of the CA reaction on the structure of the substrate.

However, the combination of the JosiPhos ligand (**L1.1**) and CuBr•SMe_2 provided high selectivity in the CA of linear alkyl Grignard reagents to a range of aliphatic linear enones in *t*BuOMe at −75 °C (Scheme 1.11).[35]

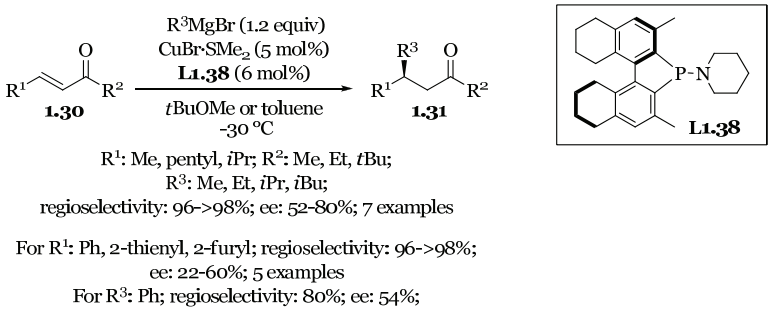
An especially notable example is the addition of MeMgBr to simple acyclic enones (Scheme 1.12). For this CA the corresponding 1,4-adducts could be obtained with 98% ee, even with a catalyst loading of 1 mol%. The scope of the Cu-catalyzed asymmetric CA includes aromatic and γ-substituted aliphatic acyclic enones.[35]

Finally, In 2008 Feringa and co-workers employed[139] the readily accessible, cheap, and easy to modify, phosphoramidites for the ACA to acyclic enones. Excellent regio- and good enantioselectivities in the range of 50-80% were achieved using aliphatic substrates and **L1.38** (Scheme 1.13). However for the addition to aryl-substituted substrates poor to moderate enantioselectivities were obtained.

Scheme 1.12. *Cu-catalyzed ACA of MeMgBr to 3-octen-2-one.*



Scheme 1.13. ACA of Grignard reagents to acyclic enones using phosphoramidite ligand **L1.38**.



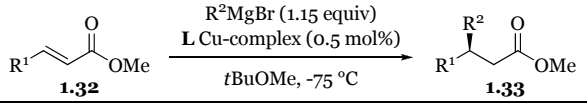
1.8.3 Catalytic ACA to esters and thioesters

Acyclic α,β-unsaturated esters are a particularly important substrate class in the CA of organometallic reagents due to the synthetic versatility of the enantiomerically enriched ester products. However, until recently progress with these substrates was limited. Use of ACA in organic synthesis has primarily relied on chiral auxiliary methods.[140] The lower intrinsic reactivity of α,β-unsaturated esters relative to the corresponding enones of the acyclic unsaturated systems may account for this paucity of versatile methods.[141]

Recent advances have shown that the ACA of alkylMgBr to linear α,β-unsaturated methyl esters catalyzed by CuBr•SMe_2 and either JosiPhos (**L1.1**) or reversed JosiPhos (**L1.31**) can provide the 1,4-addition products in high yield and enantioselectivity for a wide range of substrates (Table 1.12, next page).[142] At 0.5 mol% catalyst loading these systems allow for the addition of linear alkyl (e.g. entry 1), as well as *iso* pentyl and homoallyl Grignard reagents (entry 2 and 3), to a wide range of α,β-unsaturated methyl esters. For the less hindered electrophiles, i.e. those without branching at the γ-position, the Cu-complex of **L1.1** afforded the best results (entry 1-6). For γ-branched (entry 7) or aryl-substituted α,β-unsaturated methyl esters (entry 8 and 9) the Cu-complex of **L1.31** provided the optimum results. Importantly, the Cu-complex of **L1.1** could be recovered from the crude reaction mixture and reused repeatedly without loss of activity.[143] Furthermore, the Z-enoates afforded the opposite enantiomer of the addition product to that obtained with the *E*-enoates albeit with lower enantioselectivity (entry 10).

A limitation of this method is the addition of the relatively unreactive methyl Grignard reagent that gave high enantioselectivity (93%, entry 11) but low conversion (19%). Since the CA of MeMgBr is an important target due to its potential application in the synthesis of biologically active compounds,[58b] the more electrophilic and readily accessible α,β-unsaturated thioesters were employed.[144] With the JosiPhos (**L1.1**) ligand, the Cu-catalyzed CA of MeMgBr to a wide range of α,β-unsaturated thioesters was complete within 2 h at −75 °C (Table 1.13, next page).

Table 1.12. *Cu-catalyzed ACA of Grignard reagents to α,β-unsaturated esters.*



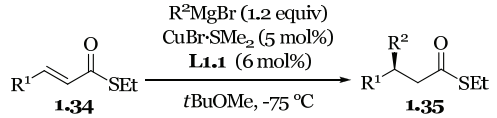
1.32 **1.33**

entry	R¹	R²	L	yield (%)[a]	ee (%)
1	Me	*n*Bu	**L1.1**	92	95
2	Me	homoallyl	**L1.1**	67	85
3	Me	*iso* pentyl	**L1.1**	90	96
4	*n*Pr	Et	**L1.1**	99[b]	93
5	CH_2OBn	Et	**L1.1**[c]	85	86
6	*i*Bu	*n*Bu	**L1.1**[c]	99[b]	92
7	cyclohexyl	Et	**L1.31**[c]	86	98
8	2-furyl	Et	**L1.31**	90	95
9	Ph	Et	**L1.31**[d]	94	98
10	Ph[e]	Et	**L1.31**[f]	90	53[g]
11	*n*Pr	Me	**L1.31**[c]	19[b]	93

[a] Regioselectivity: [1,4/(1,4+1,2)] x 100 was over 98% in all examples. [b] Conversion. [c] 2.5 mol% catalyst was used. [d] 1.5 mol% catalyst was used. [e] Addition to the *Z*-α,β-unsaturated ester. [f] 5.0 mol% catalyst and 1.5 equiv of EtMgBr were used. [g] The product has opposite configuration compared to the product obtained from addition to the *E*-α,β-unsaturated ester.

Under these conditions the β-methyl substituted thioesters **1.35** and (after methanolysis) the corresponding methyl esters were obtained with excellent enantiomeric excess (up to 96%, entries 1-6). The Cu-catalyzed CA of MeMgBr furnishes the 1,4-addition products of thioester **1.34** exclusively and in excellent yield with complete regioselectivity and in most cases with excellent enantioselectivity. Furthermore, the CA of other linear Grignard reagents, such as EtMgBr (entry 7), *n*PrMgBr (entry 8), and *n*BuMgBr (entry 9) provide

Table 1.13. *Cu-catalyzed ACA of Grignard reagents to α,β-unsaturated thioesters.*



1.34 **1.35**

entry	R¹	R²	yield (%)[a]	ee (%)
1	pentyl	Me	90	96
2	*n*Bu	Me	93	95
3	*n*Pr	Me	92	96
4	Et	Me	92	92
5	$(CH_2)_3OBn$	Me	84	95
6	Ph	Me	65	95
7	pentyl	Et	89	86
8	Et	*n*Pr	87	85
9	Me	*n*Bu	90	90
10	pentyl	*i*Pr	93	25
11	pentyl	*i*Bu	80	15

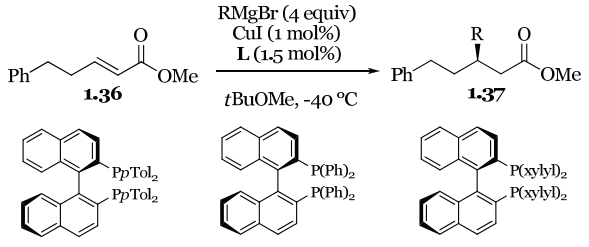
[a] Regioselectivity: [1,4/(1,4+1,2)] x 100 was over 99% in all examples.

enantioselectivities in the range of 85 to 90%. However, bulky Grignard reagents, such as *i*PrMgBr (entry 10) and *i*BuMgBr (entry 11), gave poor enantioselectivity under these conditions. The higher reaction rate observed for the methyl adducts obtained from the α,β-unsaturated thioesters compared with their respective oxoester analogs is most probably due to their inherent electronic properties. Those properties are more similar to those of the corresponding enones.[145,ii]

The complementary use of TaniaPhos (**L1.26**) and JosiPhos (**L1.1, L1.31** and **L1.32**) type ligands in combination with a Cu source have proven to be a considerable advance in the development of protocols for the CA of Grignard reagents that are directly applicable in organic synthesis.[43,116] These catalyst systems cover a broad range of substrates, such as α,β-unsaturated cyclic and acyclic enones, esters and thioesters, and provide high regio- and enantioselectivity. A further advantage of these methods is the low catalyst loading required, the use of air-stable preformed Cu^{I} complexes of the chiral ligands and the robustness of the reaction to traces of water and dioxygen, which allows these transformations to be executed outside of the glove box. That is not to say that these methods are a panacea to ACA as several challenges remain. In particular more efficient catalytic systems should be developed for the addition of Grignard reagents to several cyclic enones and for the addition of α-branched-, vinyl-, allyl- and aryl-Grignard reagents.

A complementary and efficient catalyst system for the CA of Grignard reagents to α,β-unsaturated esters was recently reported by Loh and co-workers.[146] This catalyst is based on CuI complexed with BINAP (Table 1.14, **L1.21**) or BINAP analogues (**L1.39** and **L1.40**). The ligand **L1.39** gives much better results (entry 1) than the phenyl (**L1.21**, entry 2) or xylyl analogs (**L1.40**, entry 3).

Table 1.14. *ACA of Grignard reagents to α,β-unsaturated esters catalyzed by Cu/BINAP complexes.*



entry	L	R	yield (%)[a]	ee (%)
1	**L1.39**	Et	88	93
2	**L1.21**	Et	85	85
3	**L1.40**	Et	83	48

[a] Regioselectivity: [1,4/(1,4+1,2)] x 100 was over 99% in all examples.

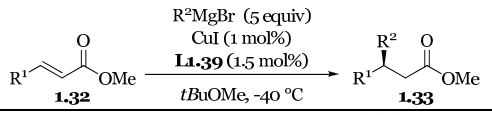
[ii] Alternatively a possible positive effect arising from a coordination of the active catalyst to the sulfur atom can not be ruled out.

Under the reaction conditions, i.e. 1.5 mol% of Tol-BINAP (**L1.39**) and 1 mol% of CuI in *t*BuOMe at −40 °C, the ACA of a range of Grignard reagents could be performed with enantioselectivity of up to 95% (Table 1.15, entries 1-9).[146] The major differences compared with the systems based on ferrocenyl phosphine ligands[121] are that higher enantioselectivity can be achieved in the CA of *i*PrMgBr and unsaturated Grignard reagents (For the ACA of MeMgBr *vide infra*).

The ACA of Grignard reagents to a number of α,β-unsaturated esters was carried out under these conditions (entries 10-17). However, reduced enantioselectivity was observed with aliphatic α,β-unsaturated esters in comparison to that obtained with the JosiPhos-based system (entries 11 and 12). Interestingly, similar enantioselectivity was obtained with both the *E*- and *Z*-methyl ester of 5-phenylpent-2-enoate (93% for *E*, entry 2 vs. 94% for *Z*, entry 14). In contrast, for the benzyloxy substituted substrate higher enantioselectivity was obtained for the *Z*-enoate (73% for *E*, entry 15 vs. 87% for *Z*, entry 16).

In an effort to improve the results of the ACA of MeMgBr to aromatic α,β-unsaturated thioesters Feringa and co-workers[147] identified Tol-BINAP/Cu as a more active catalyst compared to the JosiPhos/Cu system[144] used previously (Table 1.16, entries 1-4). Further comparison of the two catalyst systems in the ACA to α,β-unsaturated thioesters showed improved results in the addition of secondary and bulky Grignard reagents using Tol-BINAP/Cu. In contrast, for the primary organomagnesium reagents, JosiPhos/Cu was found to provide the best regio- and

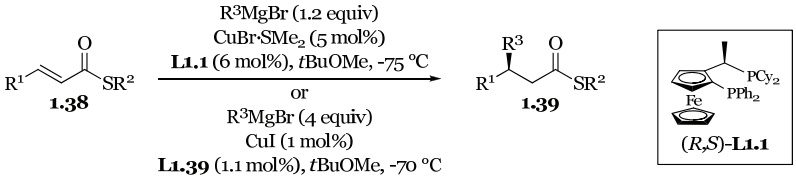
Table 1.15. *ACA of Grignard reagents to α,β-unsaturated esters catalyzed by Cu/Tol-BINAP (***L1.39***) complexes.*



entry	R¹	R²	yield (%)[a]	ee (%)
1	CH_2Bn	Me	20	98
2	CH_2Bn	Et	88	93
3	CH_2Bn	*n*Pr	90	92
4	CH_2Bn	*i*Pr	89	91
5	CH_2Bn	*n*Bu	90	92
6	CH_2Bn	pentyl	86	90
7	CH_2Bn	heptyl	89	92
8	CH_2Bn	*i*Bu	91	86
9	CH_2Bn	homoallyl	90	94
10	Me	Et	83	74
11	*n*Pr	Et	85	87
12	*i*Pr	Et	90	95
13	Ph	Et	90	93
14	CH_2Bn[b]	Et	86	94[c]
15	CH_2OBn	Et	83	73
16	CH_2OBn[b]	Et	86	87[c]
17	furyl	Et	80	85

[a] Regioselectivity of the 1,4-:1,2-addition was in all cases over 99:1. [b] Addition to the *Z*-α,β-unsaturated ester. [c] Provides a product with the opposite configuration compared to the product obtained from addition to the *E*-α,β-unsaturated ester.

Table 1.16. *ACA of Grignard reagents to α,β-unsaturated thioesters catalyzed by the Cu/JosiPhos and Cu/Tol-BINAP complexes.*



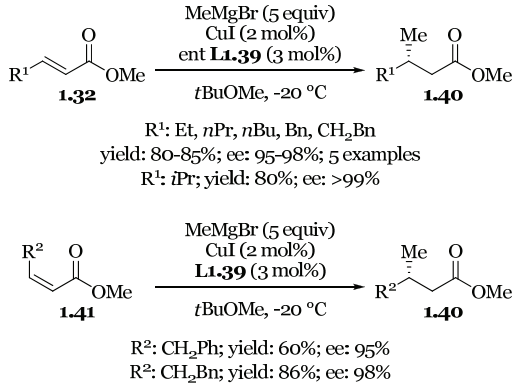
entry	R^1	R^2	R^3	Tol-BINAP (**L1.39**) yield (%)[a,b]	ee (%)	JosiPhos (**L1.1**) yield (%)[a]	ee (%)
1	Ph	Me	Me	88	94	65 (90)	95
2	*p*ClC$_6$H$_4$	Et	Me	93	99	60[c] (95)	>99[c]
3	*p*MeC$_6$H$_4$	Et	Me	34 (39)	99	33 (75)	>99
4	*p*MeOC$_6$H$_4$	Et	Me	15 (22)	96	24 (35)	93
5	pentyl	Et	*i*Pr	89	65	93	25
6	pentyl	Et	*i*Bu	95	94	80	15
7	Me	Et	*n*Bu	94	74	90	90
8	pentyl	Et	Me	90	93	90	96
9	*i*Pr	Et	Me	82	99	-	-
10	CH$_2$OTBDPS	Et	Me	95	83	95	98

[a] Regioselectivity 1,4-:1,2-addition in all cases over 99:1. [b] Conversion between parentheses, were not 99%. [c] Reaction performed on methylthioester.

enantioselectivity (entries 7 and 8). Overall, it is apparent that the TolBINAP/Cu system provides superior results in the ACA to γ-substituted aliphatic substrates (entry 9) whereas the JosiPhos/Cu catalyst is superior for δ-functionalized substrates[148] (entry 10).

Furthermore, in 2008 Loh and co-workers reported[149] the first addition of MeMgBr to α,β-unsaturated esters in high yields using Tol-BINAP (**L1.39**) and CuI. Instead of the temperature (-40 °C) previously employed to achieve ACA with the combination of this particular catalytic system,[146] elevated temperature (-20 °C) was used to obtain good yields and excellent enantioselectivities for a range of substrates (Scheme 1.14).

Scheme 1.14. *ACA of MeMgBr to α,β-unsaturated esters catalyzed by Cu/Tol-BINAP (***L1.39***) complexes.*

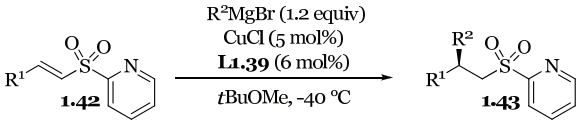


1.8.4 Catalytic ACA to other Michael acceptors

In recent years, research has shown that the ACA of Grignard reagents is not limited to enones and eno(thio)ates. Feringa and co-workers reported[150,151] the ACA to α,β-unsaturated sulfones in excellent regio- and stereoselectivities (Scheme 1.15).

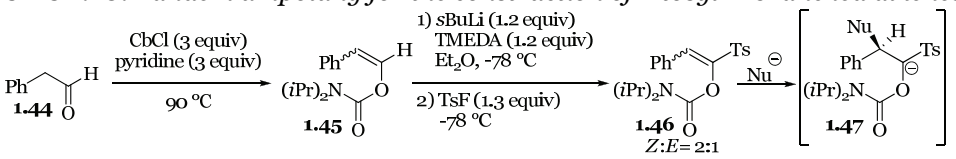
Furthermore, via tandem umpolung (Scheme 1.16) Hoppe and Chen[152] obtained 1-tosyl-2-branched alkenes in moderate enantioselectivity and good diastereoselectivity (Table 1.17). In this transformation the aldehyde **1.44** is first transformed to an electrophile (**1.45** and **1.46**), followed by the addition of a Grignard reagent to leave a nucleophilic substrate behind (**1.47**).

Scheme 1.15. *Cu-catalyzed ACA of Grignard reagents to α,β-unsaturated sulfones.*



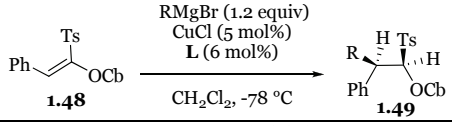
R^1: pentyl, octyl, *i*Pr, *i*Bu, cyclohexyl, $TBDPSOC_2H_4$, $BnCH_2$;
R^3: Me, Et, *n*Bu, $BnCH_2$, isoamyl;
yield: 80-97%; regioselectivity: >98%; ee: 87-94%; 12 examples

Scheme 1.16. *Tandem umpolung for the construction of 1-tosyl-2-branched alkenes.*



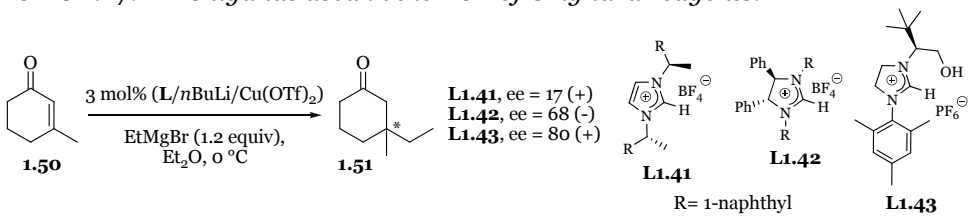
Used abbreviations; Cb=carbamate; Nu=nucleophile; Ts=tosyl.

Table 1.17. *Cu-catalyzed ACA of Grignard reagents to 1-carbamate-1-tosyl-1-alkenes.*



entry	R	L	yield (%)	ee (%)	de (%)
1	allyl	**L1.1**	70	42	90
2	allyl	**L1.35**	91	48	98
3	*iso* propenyl	**L1.1**	25	22	62

Scheme 1.17. *NHC ligands used in the ACA of Grignard reagents.*

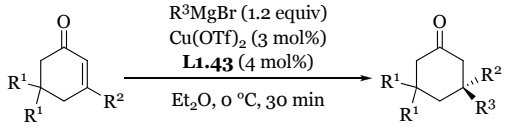


1.8.5 All C-quaternary centers through catalytic ACA

The construction of quaternary stereogenic centers is a major contemporary challenge in asymmetric catalysis.[153] In 2006 Alexakis and co-workers reported[154] that diaminocarbene based ligands (N-heterocyclic carbene ligand [NHC]) in combination with $Cu^{II}(OTf)_2$ accelerate the CA of Grignard reagents to trisubstituted cyclic enones with moderate to high enantioselectivity. This was the first example of the application of NHC ligands to the ACA of Grignard reagents. Among the chiral NHC ligands **L1.41-L1.43** tested, the most promising results were obtained with imidazolidinium ligands bearing chiral moieties at the nitrogen atoms of the heterocycle (Scheme 1.17).

$Cu^{II}(OTf)_2$/**L1.43** was identified as the most effective catalyst for this reaction. Initial studies employed *n*BuLi to deprotonate the ImH^+ unit of the ligand, however, better reproducibility could be achieved when the deprotonation was performed with the Grignard reagent itself. It was found that high enantioselectivity was obtained with primary Grignard reagents (Table 1.18, entries 1-4). However, with secondary Grignard reagents (entries 5 and 6) it was necessary to lower the temperature to −30 °C to achieve good results in the ACA reaction, while the addition of tertiary Grignard reagents does not proceed. The addition of EtMgBr was performed on a number of trisubstituted cyclohexenones affording the products with modest to good enantioselectivity (entries 8-12) and to 5- and 7-membered ring substrates reaching 46% and 82% ee, respectively. Finally, CA with PhMgBr gave modest enantioselectivity (entry 13).

Table 1.18. *NHC ligand/Cu-catalyzed ACA.*

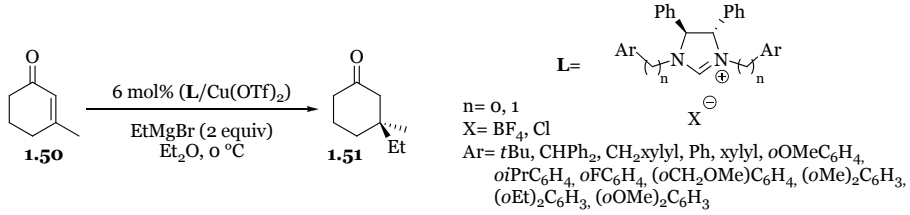


1.52 **1.53**

entry	R^1	R^2	R^3	conversion (%)	ee (%)
1	H	Et	Me	98	68
2	H	Me	*n*Bu	100	77
3	H	Me	*i*Bu[a]	100	96
4	H	Me	homoallyl[a]	91	90
5	H	Me	*i*Pr[b]	100	77
6	H	Me	cyclopentyl[a]	100	85
7	H	Me	*t*Bu[a]	0	-
8	H	Me	Et	99	80
9	Me	Me	Et	93	71
10	H	*i*Bu	Et	98	81
11	H	Ph	Et	98	72
12	H	homoallyl	Et	94	69
13	H	Me	Ph[a]	72	66

[a] Reaction performed at −30 °C. [b] Reaction performed at −18 °C.

Scheme 1.18. L1.43-*analogs used in the ACA of Grignard reagents.*

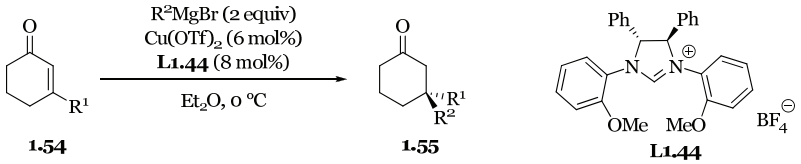


In 2008 Tomioka and co-workers[155] reported on 13 analogs of **L1.43** to construct quaternary centers via ACA using **1.50** (Scheme 1.18).

Using **L1.44** (Table 1.19) products were obtained in high yields and in ee's of up to 80%. The best results were obtained for NHC ligands incorporating aryl nitrogen substituents with a limited number of coordinating groups. Several alkyl and substituted alkyl Grignard reagents gave satisfactory ee's. However, use of MeMgBr and PhMgBr gave products with modest enantioselectivity. The obtained selectivities either compare to or are inferior to the results reported by Alexakis and co-workers.[154] However, the synthesis of the required ligands is less elaborate then the synthesis of **L1.43**.[154]

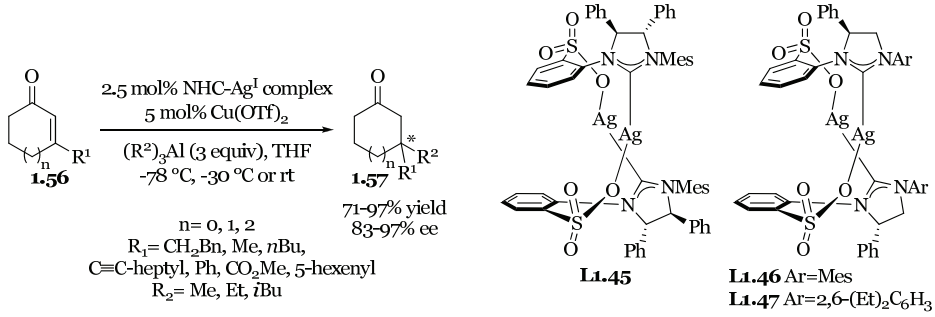
The selectivities reported by Alexakis and co-workers[154] for the asymmetric synthesis of quaternary C-centers using Grignard reagents are the highest until this date. However, using organoaluminium reagents Hoveyda and co-workers[156] and Alexakis and co-workers[157] independently reported on the efficient formation of quaternary centers on cyclic substrates by alkyl- and arylaluminium reagents. Hoveyda and co-workers[156] developed new NHC-ligands **L1.45-L1.47** to allow formation of quaternary carbon centers in high yields and enantioselectivities. Substrates bearing alkyl, aryl, alkynyl and carboxylic esters were successfully transformed in their ACA-products using commercially available Me_3Al, Et_3Al and iBu_3Al reagents (Scheme 1.19).

Table 1.19. L1.44-*catalyzed ACA to construct quaternary centers.*



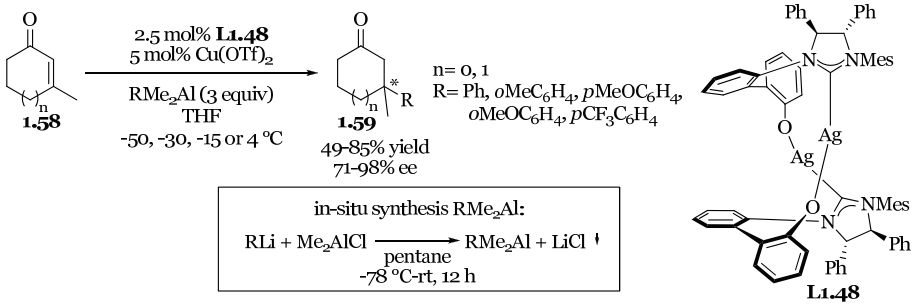
entry	R^1	R^2	T (°C)	yield (%)	ee (%)
1	Me	Et	0	94	71
2	Me	Et	-40	99	77
3	Me	Et	-60	98	80
4	Me	homoallyl	0	89	76
5	Me	*iso* pentyl	0	95	74
6	Me	*i*Bu	0	99	80
7	Me	*i*Pr	0	99	77
8	Me	Ph	0	48	34
9	Et	*i*Bu	0	65	65
10	Et	Me	0	18	18

Scheme 1.19. *Addition of alkyl-Al reagents for the formation of quaternary C-centers.*

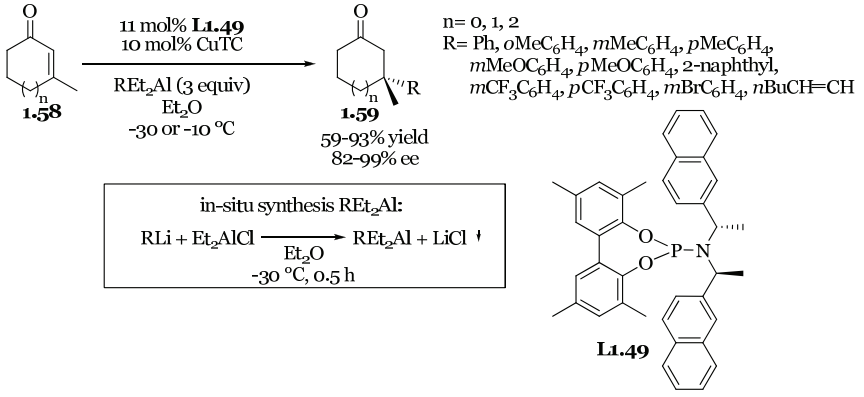


Furthermore, using **1.58**, **L1.48** and in-situ generated arylMe$_2$Al reagents (Scheme 1.20) provided products **1.59** in high yield and ee's up to 98%. Employing SimplePhos phosphoramidites (i.e. **L1.49**) Alexakis and co-workers obtained the same class of products using in-situ generated arylaluminium reagents from Et$_2$AlCl in improved ee's (Scheme 1.21).

Scheme 1.20. *Addition of in-situ formed arylaluminium reagents for the formation of quaternary C-centers using NHC-ligands.*



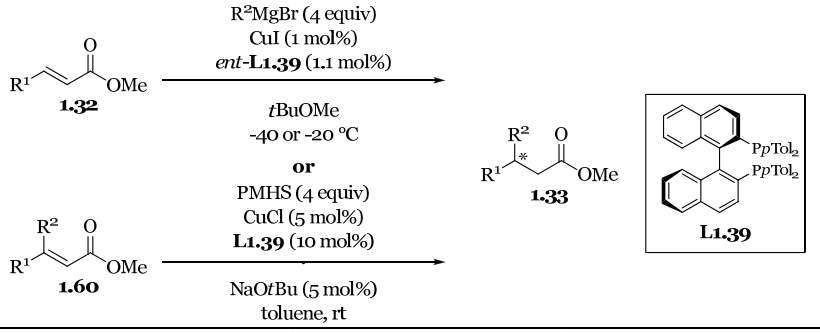
Scheme 1.21. *Addition of in-situ formed aryl-Al reagents for the formation of quaternary C-centers using SimplePhos ligands.*



1.9 Similarity between asymmetric conjugate addition of Grignard reagents and asymmetric conjugate reduction

Reactions with a congruent reaction mechanism are interesting for the development of new catalytic methods. A reaction which exhibits a large similarity with ACA is the Cu-catalyzed asymmetric conjugate reduction (ACR).[107a,b] A good example of this similarity can be found in the reduction of α,β-unsaturated esters[138] using Tol-BINAP as catalyst (Table 1.20). Using the opposite configuration of **L1.39** both the ACR with polymethylhydrosiloxane and the ACA with Grignard reagents[146,149] give products with high enantiopurity and the same absolute configuration. Although different conditions (solvent, base) are used, the mutual successful catalysis might indicate that both reactions progress via similar intermediates and that in the enantiodifferentiating step the reactions have a common intermediate (Figure 1.9).

Table 1.20. *ACA (top) versus ACR (bottom) of α,β-unsaturated esters using the Tol-BINAP ligand (***L1.39***).*



entry	R^1	R^2	*Z/E*	ee (%) ACR	*R/S*	ee (%) ACA	*R/S*
1	Ph	Et	*E*	91	*S*	93	*S*
2	CH_2Bn	Me	*E*	84	*R*	98[a]	*R*
3	CH_2Bn	Me	*Z*	83	*S*	98[a]	*S*
4	hexyl	Me	*E*	81	*R*	97[a]	*R*

[a] Using the opposite configuration of the catalyst; the opposite configuration of the product is reported. Used abbreviation; PMHS=polymethylhydroxysiloxane.

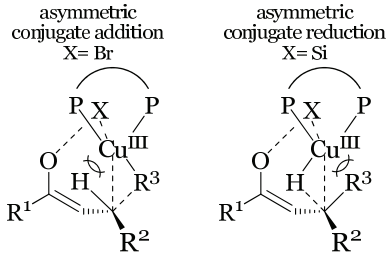
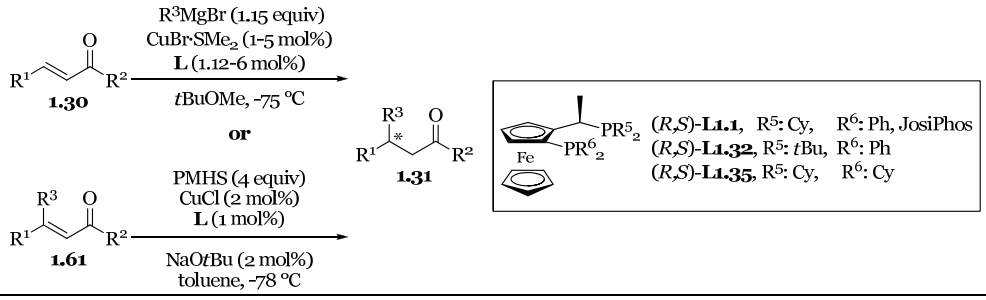


Figure 1.9. *Proposal for a common intermediate for ACR and ACA yielding the product in opposite configuration.*
A debatable chelating coordination of X to Cu is drawn[143] (for further discussion see chapter 3)

Table 1.21. *ACA (top) versus ACR (bottom) of α,β-unsaturated ketones using JosiPhos-type ligands.*



entry	R¹ ACR	R²	R³	L	ee (%) ACR	*R*/*S*	R¹ ACA	ee (%) ACA	*R*/*S*
1	$(CH_2)_4OTBDMS$	Me	Me	**L1.1**	94	*S*	*n*Bu	98	*R*
2	$(CH_2)_4OTBDMS$	Me	Me	**L1.32**	98	*S*	*n*Bu	44	*R*
3	$(CH_2)_4OTBDMS$	Me	Me	**L1.35**	55	-	*n*Bu	27	*R*

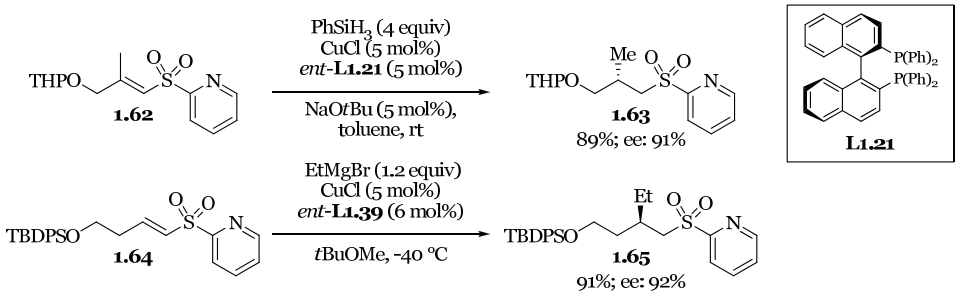
However, not all trends are the same for both the ACR and ACA of Grignard reagents. For instance, **L1.32** is very efficient for the ACR of α,β-unsaturated enones,[132e] while it is inefficient for the ACA[35] of these substrates (Table 1.21). This mismatch in efficiency might be attributed to the different conditions.

The similarity between the ACR and ACA might give leads for efficient ACA of several Michael acceptors, as is illustrated by the recent report of the ACR[158] and ACA[150] of sulfones employing similar ligands (Scheme 1.22).

Overall, taken in consideration the similarities between the ACR and ACA of Grignard reagents for the further development of ACA methods it is advisable to include several ligands which have been proven there effectiveness for ACR in ligand screenings, like 3,5-xylyl-MeO-BIPHEP[159] and DTBM-SEGPHOS.[160] Furthermore, to develop ACA of Grignard reagents for novel substrates[161] one might try β-N-substituted linear esters,[162] β-Si-substituted linear esters,[163] lactones and lactams,[164] nitriles,[165] nitroalkenes[166] and aromatic heterocycles.[167] All of these substrates have been reduced successfully in an asymmetric fashion. Vice versa, possibly, for the ACR bis-unsaturated esters might be explored for successful asymmetric 1,6-reduction.

The high similarity between ACR and ACA only holds when Grignard reagents are employed for the ACA. For instance, the most successful ligands for the ACA of Zn-reagents,[115,116,117,120] the phosphoramidites ligands, are not effective in the ACR according to Lipshutz.[107a]

Scheme 1.22. *ACR (top) versus ACA (bottom) of α,β-unsaturated sulfones.*



1.10 Cu-catalyzed asymmetric allylic alkylation with Grignard reagents

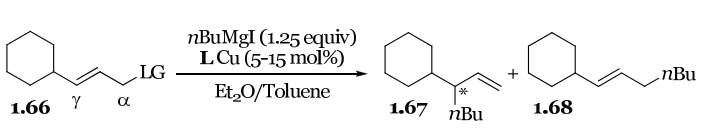
Similar to ACA, the field of AAA has advanced tremendously in the last three decades and progress has been summarized.[43,109,111,121] Most of the earlier reviews primarily deal with AAA employing a chiral catalyst. However, initial insight has been obtained by studying AAA using a stoichiometric chiral source (employing chiral substrates or chiral auxiliaries).[168]

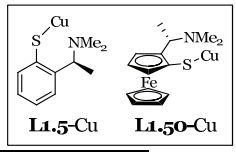
Catalytic AAA faces the same challenges as ACA. Primary requirements are to obtain synthetically useful levels of enantioselectivity and overcoming the competition of side reactions. For AAA these competing reactions are catalyzed S_N2 reactions (Scheme 1.7B) and non-catalyzed addition of highly active organometallic reagents leading to racemic products (either S_N2 or S_N2').

The development of highly enantioselective transition metal-catalyzed AAA reactions has enjoyed widespread attention over recent years.[43,109,111,121] These powerful reactions provide access to optically active building blocks frequently employed in the synthesis of complex natural products and molecules of pharmaceutical interest. In addition to the well established AAA using soft carbon nucleophiles, in recent years methods based on the use of enolates and hard organometallic based carbon nucleophiles have emerged.[43,109,111,121]

The first breakthrough in Cu-catalyzed AAA reactions with Grignard reagents was reported in 1995 by Bäckvall, Van Koten and co-workers.[169] The addition of *n*BuMgI to substrate **1.66** in the presence of a catalytic amount (14 mol%) of an arenethiolato-Cu species (**L1.5**-Cu) provided the branched product **1.67** in quantitative yield with excellent regioselectivity and moderate enantioselectivity (42%, Table 1.22, entry 1). As with the ACA reaction, the AAA reaction proved to be sensitive to changes in temperature, order of addition of the reagent, solvent, ligand/metal ratio and the coordinating abilities of the leaving group in terms of both regio- and enantioselectivity (entries 2-4). Subsequently, these results were improved upon using a ferrocene thiolato-Cu (**L1.50**-Cu) catalyst providing **1.67** in

Table 1.22. *Cu-catalyzed AAA of nBuMgI to* ***1.66*** *using* ***L1.5****-Cu or* ***L1.49****-Cu.*





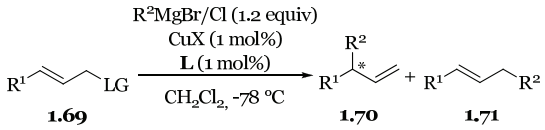
entry	LG	L	yield (%)	γ:α	ee (%)
1	OAc	**L1.5**	100	100:0	42
2	OCO(*t*Bu)	**L1.5**	100	100:0	25
3	$OPO(OEt)_2$	**L1.5**	100	92:8	10
4	$OCOCF_3$	**L1.5**	81	90:10	9
5[a]	OAc	**L1.50**	88	98:2	64

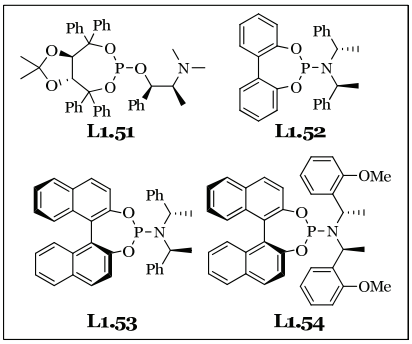
[a] 1.5 equiv of *n*BuMgI was used.

good yield, excellent regioselectivity and 64% ee (entry 5).[170] Extensive structural modification of the ferrocenyl moiety in **L1.50**-Cu has thus far proven to be unsuccessful in increasing the enantioselectivity of the reaction.[171] Subsequent studies focused initially on the use of R_2Zn reagents for AAA. High enantioselectivity was achieved with several acyclic substrates and dialkylzinc reagents.[109d,172]

Alexakis *et al.*[173] have studied several ligand classes including phosphites and phosphoramidites to address the selectivity issues impeding the development of the Cu-catalyzed AAA of Grignard reagents. Phosphite ligand **L1.51**, CuCN and EtMgCl at −78°C in CH_2Cl_2 provided quantitative conversion of substrate **1.69** to **1.70** with excellent regioselectivity albeit in racemic form (Table 1.23, entry 1). Further studies showed that for R¹= Ph and LG= Cl, the AAA could proceed in high yield, high regio- and good enantioselectivity (94% yield, 94:6 regioselectivity, 73% ee, entry 2). The enantioselectivity could be improved further by using CuTC (Cu(I) thiophene-2-carboxylate) instead of CuCN, providing AAA products with enantioselectivity of up to 82% (entry 3). The complex formed from ligand **L1.51** and CuTC proved to be an effective catalyst for S_N2'-substitution with several linear and secondary Grignard reagents with typically ca. 50% enantioselectivity. Further studies[174] revealed that **L1.52** performed better than **L1.51** when secondary Grignard reagents were used (entry 4 vs. 3 and entry 6 vs. 5) and branched products were obtained in high yields and enantioselectivity. The highest selectivity was obtained using the phosphoramidite ligand **L1.53** (entry 7).

Table 1.23. *Cu-catalyzed AAA with phosphite and phosphoramidite ligands.*



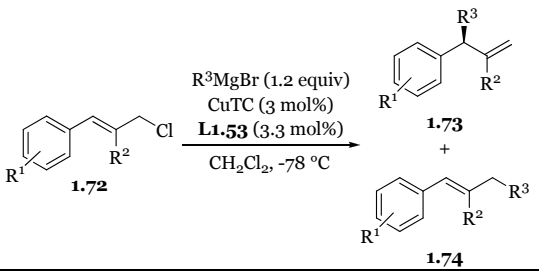


entry	R¹	LG	R²	X	L	yield (%)	γ:α	ee (%)
1	cyclohexyl	OAc	Et	CN	**L1.51**	100	100:0	0
2	Ph	Cl	Et	CN	**L1.51**	94	94:6	73
3	Ph	Cl	Et	TC	**L1.51**	97	94:6	82
4	*p*MeOC$_6$H$_4$	Cl	*i*Pr	TC	**L1.52**	98	91:9	86
5	cyclohexyl	Cl	*i*Pr	TC	**L1.51**	100[a]	83:17	13
6	cyclohexyl	Cl	*i*Pr	TC	**L1.52**	95	99:1	68
7	cyclohexyl	Cl	*i*Pr	TC	**L1.53**	100[a]	99:1	74
8	Ph	Cl	Et	TC	**L1.54**	86[a]	99:1	96
9	Ph	Cl	4-pentenyl	TC	**L1.54**	81[a]	91:9	96
10	cyclohexyl	Cl	Et	TC	**L1.54**	82[a]	>99:1	91
11	Ph	Cl	Me	Br	**L1.54**	100[a]	89:11	96

[a] Conversion.
Abbreviation used; TC=thiophene-2-carboxylate.

The observation that phosphoramidite copper complexes were catalyzing AAA with high levels of regio- and enantioselectivity prompted an in depth investigation of this class of ligands. Alexakis and co-workers reported[175] that with **L1.54** a selective Cu-catalyzed AAA reaction occurs with an enantioselectivity as high as 96% when the substrate cinnamyl chloride is used (Table 1.23, previous page, entries 8 and 9). A range of linear Grignard reagents could be used with excellent regio- and enantioselectivity. Cyclic aliphatic substrates were converted into the desired branched products with only a slight decrease in enantioselectivity (entry 10). Substitution with MeMgBr remained problematic as experienced for the ACA reaction.[144] Although MeMgBr substitution products were obtained generally with excellent enantioselectivity, the regioselectivity in all cases was moderate. Slow addition of MeMgBr over the course of several hours served to increase the regioselectivity typically from 40/60 to 85/15 ratios in favor of the optically active branched products (γ:α 89:11, entry 11) for aromatic substrates bearing either electron-withdrawing and donating substituents.[176] It was proposed that this experimental protocol avoids the formation of Gilman type cuprates that may lead to a loss of selectivity.[177] The scope of the reaction was extended to β-disubstituted allylic halide substrates[178] (Table 1.24). A series of biphenol- and binaphthol-based phosphoramidite copper complexes were tested in the AAA to β-methylcinnamyl chloride with slow addition of EtMgBr. The products were formed with varying γ:α ratios and a high enantiomeric excess (up to 98% ee, entry 1) was obtained with **L1.53** CuTC. Other Grignard reagents provided the branched products with equally good results (entry 2-4).

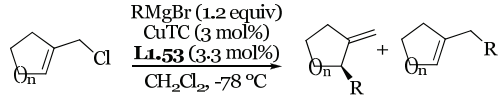
Table 1.24. *Cu-catalyzed AAA of β-disubstituted allylic chlorides.*



entry	R¹	R²	R³	yield (%)	γ:α	ee (%)
1	H	Me	Et	87	92:8	98
2	H	Me	pentyl	83	83:17	96
3[a]	H	Me	homoallyl	99[b]	89:11	97
4	H	Me	4-pentenyl	87	87:13	96
5	*p*Cl	Me	Et	87	92:8	96
6	*p*Me	Me	Et	85	84:16	96
7	H	Et	Et	83	83:17	92

[a] Slow addition of Grignard reagent. [b] Conversion.

Table 1.25. *Cu-catalyzed AAA of cyclic β-disubstituted allylic chlorides.*



1.75 **1.76** **1.77**

entry	n	R	yield (%)	γ:α	ee (%)
1	1	hexyl	91	98:2	98
2	1	CH_2Bn	99[a]	97:3	98
3	1	$(CH_2)_4OtBu$	60	98:2	97
4	2	hexyl	83	97:3	98
5	2	homoallyl	67	97:3	99
6	2	$BnCH_2$	78	85:15	99
7	3	$BnCH_2$	87	95:5	97

[a] Conversion.

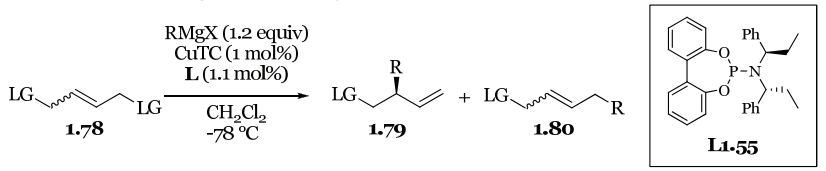
Electron donating and withdrawing substituents on the aromatic ring were tolerated providing the products in good yield, γ:α ratio and enantioselectivity (entry 5, 6). For R^2 = Et, the reaction proceeded as for the methyl substituted substrate (entry 7). For another class of β-disubstituted allylic substrates, the aliphatic endocyclic allylic chlorides, the addition of a range of Grignard reagents with 3 mol% of the copper catalyst proceeded selectively towards γ-substitution and delivered products in excellent enantiomeric excess (up to 99%). For the five-membered-ring substrate **1.75**, the ee (98%) obtained was not dependent on the Grignard reagent used (Table 1.25, entries 1-3).

Six- and seven-membered-ring allylic chlorides were converted with equally good γ:α ratios and enantioselectivity (entries 4-7). The selectivity obtained for six-membered-ring allylic chlorides was the highest using substrate **1.75** and homallylMgBr (entry 5).

Simple difunctionalized substrates used in this transformation offer considerable versatility towards further synthetic applications.[179] In particular the 1,4-*bis*-halo-2-butenes **1.78** provide valuable synthetic intermediates after AAA. *E*- and *Z*-isomers of 1,4-*bis*-halo-2-butene **1.78** were examined in the AAA with cyclohexylMgCl catalyzed by a biphenol- or binaphthol-based phosphoramidite CuTC complex. The combination of *E*-1,4-*bis*-halo-2-butene and CuTC **L1.55** (3 mol%) provided **1.79** in good yield, full regioselectivity and 77% ee (Table 1.26, next page, entry 1).

Allylic alkylation of *Z*-**1.78** generally provided products in significantly lower ee compared to *E*-**1.78** (entry 2 vs. 3). Several primary Grignard reagents could be used providing good enantioselectivity of up to 85% ee (entries 4-6) in the AAA of substrate **1.78** with **L1.53** or **L1.54**. Allylic substitutions performed on *E*-dibromo-2-butene gave similar or better results in terms of enantioselectivity than the *E*-dichloro-2-butene with phosphoramidite **L1.53** and **L1.54**. The highest selectivity was obtained using CuTC **L1.54** (3 mol%) yielding **1.79** in 70% yield and 94% ee (entry 7). When dialkylzinc reagents were employed instead of the Grignard reagents, products were obtained with moderate ee (typically 50%). Finally, substituted 1,4-bishalo-2-butenes gave a reasonable regioselectivity towards formation of the tertiary center, albeit with moderate ee's (Scheme 1.23, next page).

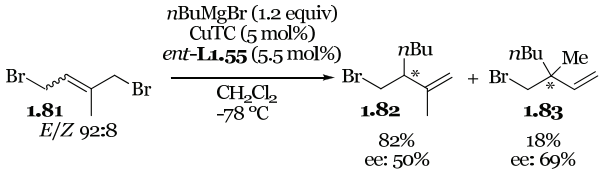
Table 1.26. *Cu-catalyzed AAA of* 1,4-bishalo-2-butenes.



entry	**1.78**	LG	R	X	L	yield (%)[a]	ee (%)
1	*E*	Cl	cyclohexyl	Cl	**L1.55**[b]	>99[c]	77
2	*E*	Cl	cyclohexyl	Cl	**L1.53**	98	75
3	*Z*	Cl	cyclohexyl	Cl	**L1.53**	87[c]	31
4	*E*	Br	$BnCH_2$	Br	**L1.53**	94	83
5	*E*	Br	*n*Bu	Br	**L1.54**	80	87
6	*E*	Cl	$(CH_2)_4O$*t*Bu	Br	**L1.54**	77	92
7	*E*	Br	$(CH_2)_2CH=C(CH_3)_2$	Br	**L1.54**	70	94
8	*E*	Br	*i*Bu	Br	**L1.53**	79	85

[a] In all cases γ:α 100:0. [b] 2 mol% of catalyst was used. [c] Conversion.

Scheme 1.23. *Cu-catalyzed AAA of substituted 1,4-bishalo-2-butenes.*

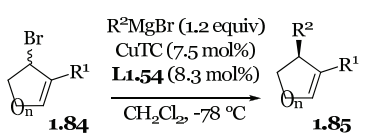


The facile conversion of the remaining chloride or bromide functionalities, e.g. via the Finkelstein reaction with NaI, demonstrated the synthetic versatility of products obtained via this route.

Recently, Alexakis and co-workers[180] reported the kinetic resolution via AAA of cycloalkenyl halides. This paper is the first report of a Cu-catalyzed AAA with Grignard reagents on secondary allylic halides with ee's over 90% (Scheme 1.25). The scope of this transformation is limited to cyclo-1-hexenylbromides in combination with alkyl Grignard reagents.

The potential of providing useful chiral building blocks for complex molecule synthesis from the Cu-catalyzed AAA to linear substrates is evident from the results in Tables 1.23, 1.24 and 1.26. However, the conversion of simple linear aliphatic substrates to yield optically active acyclic building blocks was lacking until recently. Feringa and co-workers have employed the ACA catalyst derived from JosiPhos (**L1.1**)/CuBr•SMe_2 (*vide infra*) (5 mol%) as a catalyst in *t*BuOMe for the AAA of cinnamyl bromide **1.86** with MeMgBr, affording the corresponding products with good regio- and enantioselectivity (Scheme 1.25).[181]

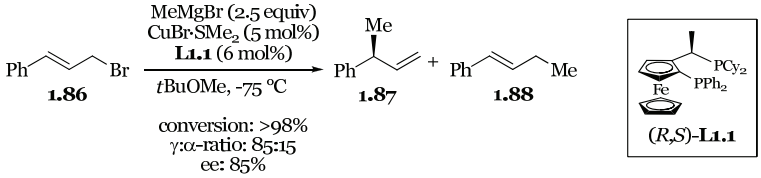
Scheme 1.24. *Cu-catalyzed kinetic AAA of cycloalkenyl halides.*



n: 2; R^1: H;
R^2: Et, *n*Bu, *t*BuO*n*Bu, $BnCH_2$;
yield: 79-95%; ee: 90-92%; 4 examples

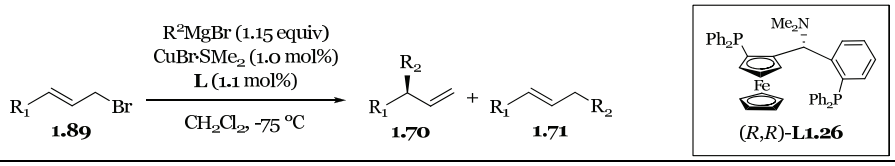
for n: 1; R^1: H; R^2: $BnCH_2$; yield: 93%; ee: 44%
for n: 3; R^1: H; R^2: $BnCH_2$; yield: 98%; ee: 38%
for n: 1; R^1: Me; R^2: $BnCH_2$; yield: 95%; ee: 18%

Scheme 1.25. *Addition of MeMgBr to cinnamyl bromide* **1.86**.



When other Grignard reagents such as EtMgBr (Table 1.27, entry 1) or aliphatic allylic bromides were applied, the regio- and enantioselectivity of the reactions were significantly lower. Only a moderate increase in the selectivity of these transformations was obtained through optimization of reaction conditions. With the related TaniaPhos ligand (**L1.26**, 6 mol%) and CuBr•SMe_2 (5 mol%) the allylic alkylation of substrates **1.89** with EtMgBr in *t*BuOMe provided only modest regioselectivity and an ee of 32% (entry 2). The selectivity was improved considerably using CH_2Cl_2 instead of *t*BuOMe, providing the desired γ-substituted product in high yield, good regioselectivity and excellent enantioselectivity (92%, 81:19 and 95%, respectively, entry 3). Catalyst loadings could be reduced to 1 mol% without affecting the selectivity. Under these conditions a series of aryl substituted allylic bromides were converted using EtMgBr with comparable selectivity. Furthermore, the allylic substitution of **1.89** could be performed with *n*BuMgBr (entry 4) and unsaturated Grignard reagents (entry 5), providing the corresponding products with excellent enantioselectivity (up to 95% ee) and good regioselectivity (up to 91:9). Importantly, MeMgBr was used successfully as a nucleophile with almost complete control of regio- and enantioselectivity (entries 6-9).

Table 1.27. *Cu-catalyzed AAA with ferrocenyl based ligands.*



entry	R^1	R^2	L	yield (%)	γ:α	*ee* (%)
1[a,b]	Ph	Et	**L1.1**	>98[c]	38:62	56
2[a,b]	Ph	Et	**L1.26**	>98[c]	31:69	32
3[a]	Ph	Et	**L1.26**	92	81:19	95
4	Ph	*n*Bu	**L1.26**	92	87:13	94
5	Ph	homoallyl	**L1.26**	93	91:9	95
6	Ph	Me	**L1.26**	91	97:3	98
7	*p*ClC_6H_4	Me	**L1.26**	95	99:1	97
8	*p*$CO_2MeC_6H_4$	Me	**L1.26**	94	98:2	97
9	1-naphthyl	Me	**L1.26**	87	>99:1	96
10	*n*Bu	Me	**L1.26**	99	>99:1	92
11	*n*Bu	Et	**L1.26**	99	>99:1	93
12	CH_2OBn	Me	**L1.26**	94	>99:1	92
13[a]	$CH_2OTBDPS$	Me	**L1.26**	72	>95:5	94
14	$CH_2N(Ts)Boc$	Me	**L1.26**	96	>95:5	95

[a] 5 mol% catalyst. [b] Reaction in *t*BuOMe. [c] Conversion.

The TaniaPhos-based catalyst proved particularly effective in the AAA of linear aliphatic allylic bromides affording almost exclusively γ-products with an enantioselectivity of up to 93% (entries 10 and 11). The synthetic applicability of Cu-catalyzed AAA reactions was enhanced further by performing this transformation on protected substrates containing oxygen or nitrogen groups.[182] In those cases products were obtained with high yields, near complete regioselectivity and in excellent enantioselectivity (entries 12-14). Several of these reactions were performed on a preparative scale (7.5 mmol) without loss of yield, regio- or enantioselectivity. The presence of a benzyloxy group is tolerated and the substitution could be performed with a wide range of linear (Me, Et, *n*Bu and pentyl) and functionalized (homoallyl and phenylethyl) Grignard reagents with equal efficiency. The bulky TBDPS protecting group was tolerated (entry 13) and in the case of MeMgBr led to even higher enantioselectivity (94%), albeit with slightly lower yields (72%) compared to benzyl protected substrates. A double protected amine moiety is also compatible with this catalyst system (entry 14)

Feringa and co-workers have investigated AAA to functionalized substrates bearing heteroatoms at the γ-position instead of the δ-position.[183,184] This reaction, the so-called *hetero*-asymmetric allylic alkylation (*h*-AAA), is fundamentally different compared to other allylic substitutions reported in the literature[43,109,111,121] since the heteroatom is connected directly to the olefinic bond (Figure 1.10).

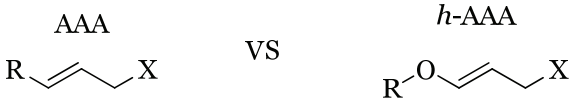
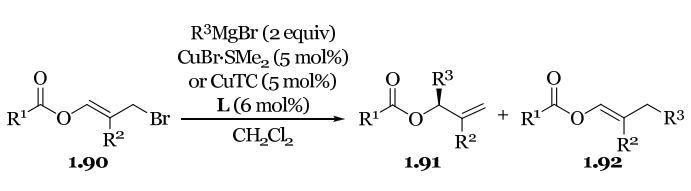


Figure 1.10. The substrates for *asymmetric allylic alkylation (AAA) and hetero-asymmetric allylic alkylation (h-AAA).*

The catalyzed allylic alkylation of **1.90** (R^1= Ph, R^2= H) with MeMgBr provided the γ-product 1-buten-3-ol ester **1.91**, the most simple chiral allylic alcohols, in 85% yield, 98% ee (Table 1.28, **1.91**, entry 1) and with complete regioselectivity. Although, typically 5 mol% catalyst loading was employed, the catalyst loadings could be reduced to as low as 0.05 mol% without a decrease in either yield, regio- or stereoselectivity.

Surprisingly, the use of *t*BuOMe as the solvent led largely (entry 2) to the formation of the undesired α–regioisomer at a relatively low rate (36% conversion, 12 h). Furthermore, an intriguing example of a reversal in regioselectivity was observed when the reaction was carried out below −80°C. Whereas at −74°C the reaction provides exclusively the γ-product, at lower temperatures the undesired S_N2 product is formed in increasing amounts (entries 1, 3 and 4). Formation of both the γ- and α-substituted allylic esters appears to be Cu-catalyzed since in the absence of copper neither of these products was formed. At higher temperatures the

Table 1.28. *Cu-catalyzed h-AAA with Grignard nucleophiles.*

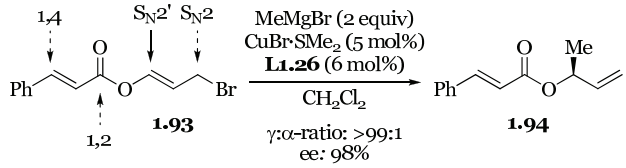


entry	R^1	R^2	R^3	L	temp (°C)	yield (%)	γ:α	ee (%)
1	Ph	H	Me	**L1.26**	-74	85	99:1	98 (+)
2[a]	Ph	H	Me	**L1.26**	-73	36	8:92	-
3	Ph	H	Me	*ent*-**L1.26**	-82	67	79:21	94 (-)
4	Ph	H	Me	**L1.26**	-85	76	37:63	-
5	Ph	H	Me	**L1.26**	-15	76	99:1	90 (+)
6	Ph	H	Et	**L1.26**	-75	87	>99:1	98
7	Ph	H	homoallyl	**L1.26**	-75	96	>99:1	97
8	Ph	H	CH_2Bn	**L1.26**	-75	93	>99:1	93
9	Ph	H	octadecanyl	**L1.26**	-75	93	>99:1	>95
10	Ph	Me	Et	**L1.53**	-75	97	2.5:1	97
11	Ph	Me	pentyl	**L1.53**	-75	96	2:1	97
12	styryl	H	Me	**L1.26**	-73	80	>99:1	98
13	styryl	H	Et	**L1.26**	-73	80	>99:1	98

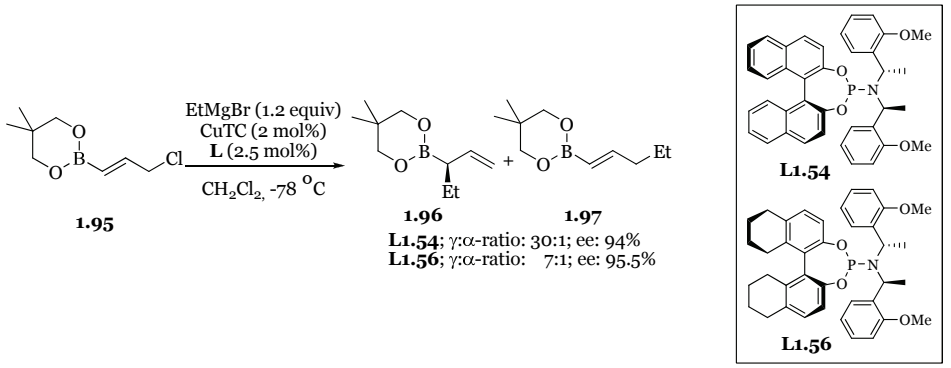
[a] Reaction in *t*BuOMe.

enantioselectivity was largely preserved (90% ee, −15 °C, entry 5). A range of Grignard reagents containing simple alkyl moieties, long alkyl chains and unsaturated alkyl groups were used successfully with excellent regio- and enantioselectivity (entries 6-9). However, the catalyst derived from CuBr•SMe_2 and TaniaPhos (**L1.26**) did not provide S_N2'-substitution with sp^2-hybridized, secondary and bulky Grignard reagents. β-Substituted substrates provided predominantly **1.92**, but a combination of ligand **L1.53** with CuTC and slow addition of the Grignard reagent, presumably preventing the formation of Gilman type cuprates, again resulted in high yield and high ee but with modest regioselectivity (entries 10 and 11). The excellent γ-selectivity of the catalyst system was illustrated with cinnamyl derivatives **1.93** which can undergo 1,4-addition, 1,2-addition, S_N2' and S_N2 substitution (Scheme 1.26). This catalyzed conversion provided exclusively the S_N2'-products (i.e. **1.94**), with excellent regio- and enantioselectivity (entries 12-13).

Scheme 1.26. *Possible modes of addition/substitution for the reaction of MeMgBr on the cinnamyl derivative* **1.93** *and the selectivity observed.*



Scheme 1.27. *Cu-catalyzed h-AAA to allylic boronates.*

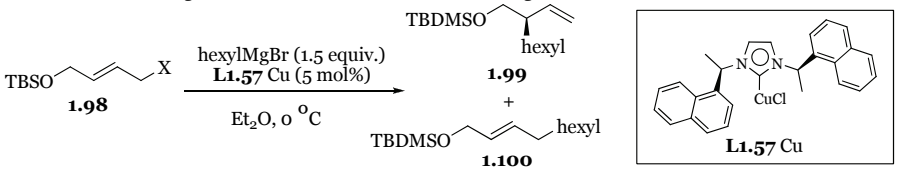


Recently Carosi and Hall reported[185] a method for the *h*-AAA reaction using 3-halopropenylboronates as substrates. The highest enantioselectivity was obtained using CH_2Cl_2 as the solvent with slow addition of EtMgBr as the nucleophilic reagent and with CuTC as the Cu source (Scheme 1.27).

The ligands **L1.54** or **L1.56** (5.5 mol%), CuTC (5 mol%) with 2,2-dimethylpropanediol boronate provided the γ-product with excellent selectivity. Carousi and Hall reported a dependency on the counter ion. For instance, 3-bromopropenylboronates provided lower enantioselectivity and lower γ:α ratios. Furthermore, a one-pot procedure was developed for the stereoselective aldehyde allylation based on the γ-product. This procedure yielded homoallylic alcohols with near perfect chirality transfer.

Okamoto and co-workers reported the AAA reactions of Grignard nucleophiles using catalysts derived from CuCl and C2-symmetric NHC ligands.[186,187] Treatment of 4-siloxy-2-buten-1-ol derivative **1.98** with hexylMgBr in the presence of copper complexes of chiral NHC ligands (**L1.57**, 5 mol%) in Et_2O at 0 °C provided the S_N2'-products **1.99** quantitatively, albeit with low to moderate ee (Table 1.29).

Table 1.29. *Cu-catalyzed AAA with chiral NHC ligands.*

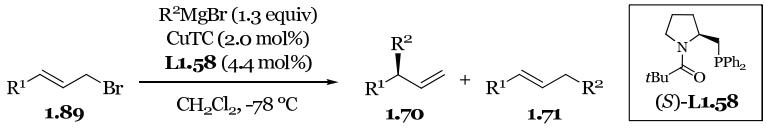


entry	**1.98**	X	γ:α	ee (%)
1	*E*	OAc	95:5	60 (*R*)
2	*E*	$OCONMe_2$	99:1	55 (*R*)
3	*E*	O-(2-pyridyl)	98:2	70 (*R*)
4	*Z*	O-(2-pyridyl)	86:14	60 (*S*)

Catalysts with sterically demanding N-substituents gave the highest levels of asymmetric induction. Introduction of additional C2-chirality into the heterocyclic component of NHC resulted in either an inversion or a decrease in the enantioselectivity obtained. Allylic acetates and 2-pyridyl ethers were appropriate leaving groups in the substrates suitable for this catalytic system (entries 1, 3 and 4), whereas carbamates (entry 2), carbonates and chlorides provided products with low ee. Inversion of product configuration was observed when *E*-allylic substrates were used instead of the *Z*-isomers (entry 3 vs. 4).

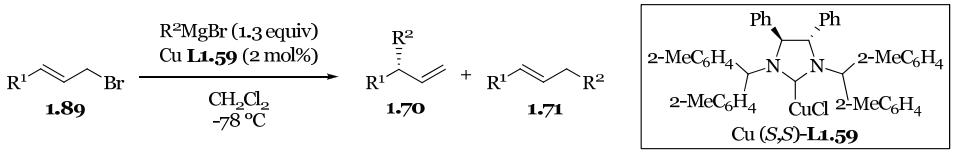
The scope of the Cu-catalyzed AAA had so far been limited to alkyl Grignard reagents. Recently, Tomioka and co-workers reported an amidophosphane ligand (**L1.58**) which allows the addition of ArMgBr to aliphatic allylic bromides[188] in reasonable to excellent regioselectivity and moderate to good enantioselectivity (Scheme 1.28). Furthermore they described the use of an NHC ligand (**L1.59**) for efficient arylation of cinnamyl bromides using Grignard reagents[189] in excellent regio- and enantioselectivity (Scheme 1.29). Especially, the enantioselective preparation of the important diaryl substituted trisubstituted carbon is an important breakthrough.

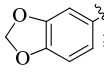
Scheme 1.28. *Cu-catalyzed AAA of ArMgBr with a chiral amidophosphane ligand.*



R^1: Et, pentyl, CH_2Br; R^2: Ph, pFC_6H_4;
yield: 81-100%; regioselectivity: 52-100%; ee: 67-81%; 4 examples

Scheme 1.29. *Cu-catalyzed AAA of ArMgBr to cinnamyl bromides with a chiral NHC-Cu complex.*



R^1: $pClC_6H_4$, $mClC_6H_4$, $oClC_6H_4$, $pCF_3C_6H_4$, $mpCl_2C_6H_3$, $oMeC_6H_4$, $oMeOC_6H_4$;
R^2: Ph, pFC_6H_4, $pClC_6H_4$, $pMeC_6H_4$;
yield: 91-99%; regioselectivity: 86-94%; ee: 92-98%; 13 examples
for R^1=1-naphthyl; R^2=Ph; yield:97%; regioselectivity: 50%; ee: 93%
for R^1= $oClC_6H_4$; R^2=  ; yield:68%; regioselectivity: 94%; ee: 92%

1.11 Outlook

As is evident from the literature presented in paragraph 1.8 and paragraph 1.10 the field of Cu-catalyzed ACA and AAA using Grignard reagents is quite advanced. However, a wide variety of unexplored substrates can be investigated for ACA and AAA using Grignard reagents. This thesis is focused on exploring challenging substrates in which multiple chemo-, regio- and stereochemical issues arise. Furthermore, all of the new methodology described in this thesis leads to interesting multifunctional building blocks. In addition to the synthetic use, the research has been directed to allow further exploration of the mechanism of these important transformations (see respectively chapter 3 and 5 for an introduction on the mechanism of ACA and AAA using Grignard reagents).

The first part of this thesis deals with multiple unsaturated Michael acceptors as substrates for ACA with Grignard reagents. In chapter 2 the development of the first method for enantioselective 1,6-addition primarily dictated by the catalyst is described, for which further regioselectivity issues, compared to 1,4-ACA, had to be solved. Then in chapter 3, initial and primarily structural studies towards a mechanism for the 1,6-ACA are reported. Finally, the synthetic application of the 1,6-ACA for the construction of deoxypropionate units is explored in chapter 4.

In the second part of this thesis 4-halocrotonates are explored as substrates. These substrates possess all structural features to either allow AAA or ACA. In chapter 5 the selective AAA of MeMgBr, leading to highly warranted α-Me substituted esters, is described. The products are then further elaborated to multifunctional building blocks. The selective ACA of Grignard reagents to 4-halocrotonates is described in chapter 6. Via an ACA-enolate trapping sequence this transformation yields functionalized cyclopropanes.

Finally, in chapter 7 a summary of the current status of the field of ACA and AAA using Grignard reagents is given and the further perspectives of this field are discussed.

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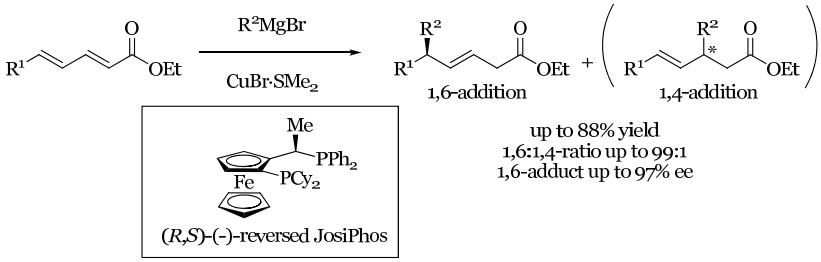
Chapter 2

Catalytic Enantioselective 1,6-Conjugate Addition of Grignard Reagents to Linear Dienoates, Dienothioates and Dienones

In this chapter the catalytic enantioselective 1,6-addition of Grignard reagents to several acyclic α,β,γ,δ-unsaturated Michael acceptors nonsubstituted at the β- and monosubstituted at the δ-positions is described. In this transformation, both regio- and enantioselectivity are dictated by Cu-catalysis using the reversed JosiPhos ligand. A variety of alkyl Grignard reagents were added in a 1,6-fashion to several alkyl-substituted α,β,γ,δ-bisunsaturated esters in good yield (up to 88%) and excellent regio- (up to 99:1) and enantioselectivity (up to 97% ee). A limitation of the current methodology is the combined use of reactive Grignard reagents and active Michael acceptors (bisunsaturated thioesters and ketones) for asymmetric 1,6-addition which gives significantly lower regio- and enantioselectivity.



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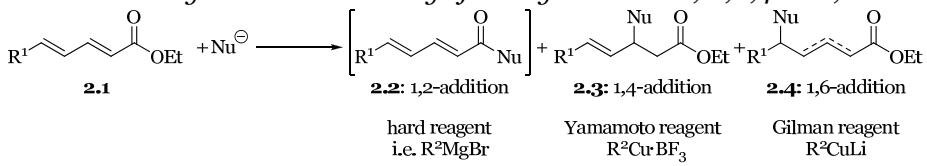
2.1 Controlling regio- and stereoselectivity for addition to α,β,γ,δ-bisunsaturated Michael acceptors

Achieving selectivity (chemo-, regio- as well as stereoselectivity) has always been a major challenge in organic synthesis.[1] This is particularly evident for conjugate addition reactions (CA), one of the prominent methods to form C-C bonds.[2] In the enantioselective version of this reaction, the asymmetric conjugate addition (ACA),[3] besides high regioselectivity (1,4- vs. 1,2-addition), excellent control of stereoselectivity has been achieved.

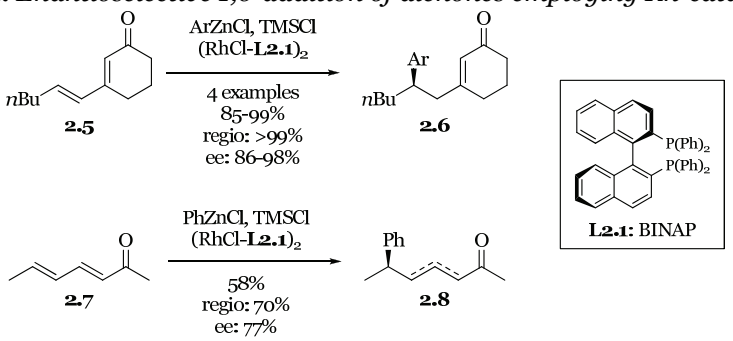
Compared to 1,4-ACA, conjugate addition to extended Michael acceptors[4] requires additional control of regioselectivity. For bisunsaturated Michael acceptors tuning of the electron density on the copper reagent allows regioselective 1,4-[5] or 1,6-addition[6,7] (Scheme 2.1) as shown in pioneering work by Yamamoto (for dienoates)[5] and Krause (for enynes).[7]

Scheme 2.1. *Tuning the electron density of a reagent allows 1,2-, 1,4- or 1,6-addition.*

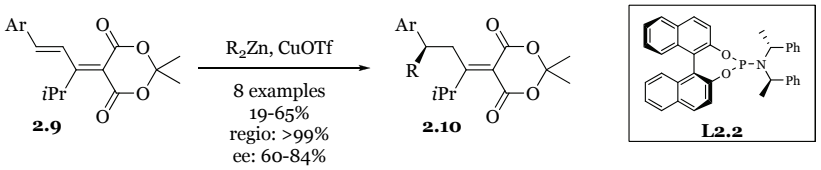


Recently, other metals including Fe,[8] Rh[9] and Ir[10] have been employed to obtain 1,6-addition products using either organometallic reagents[8] or boronic acids.[9,10] However, only slight progress has been made in enantioselective extended conjugate additions (that is addition farther away from the electron withdrawing group than the 1,4-addition) to dienones and dienoates.[11] In 2005 Hayashi et al.[12] succeeded in the arylation of selected β-substituted dienones in an asymmetric fashion employing Rh-catalysis and BINAP (**L2.1**) as ligand (Scheme 2.2). In 2006 Fillion et al.[13] reported the 1,6-ACA of dialkylzinc reagents to Meldrum's acids with good selectivity (Scheme 2.3). Recently, Jørgensen and co-workers[14] disclosed the ACA of different nucleophiles (β-ketoesters and a glycine imine ester) to a variety of δ-unsubstituted dienones and dienoates employing a dihydrocinchonine type organocatalyst (Scheme 2.4).

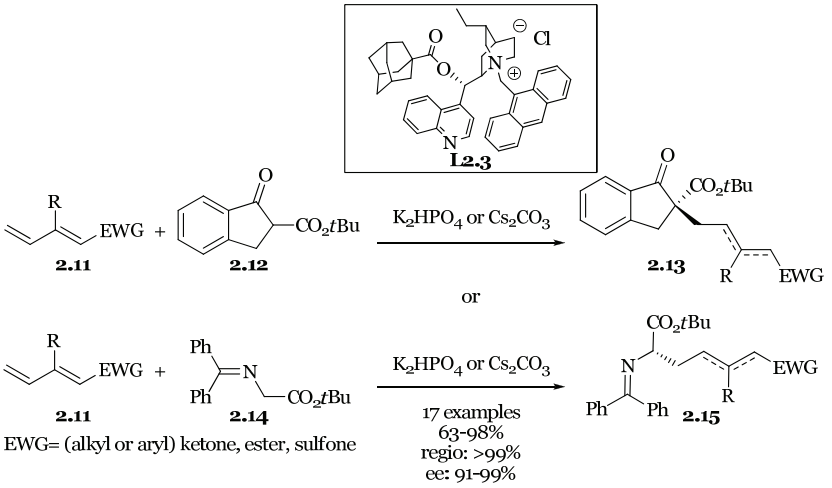
Scheme 2.2. *Enantioselective 1,6-addition of dienones employing Rh-catalysis.*



Scheme 2.3. *Asymmetric 1,6-addition of β-disubstituted Meldrum's acids derivatives.*



Scheme 2.4. *Enantioselective 1,6-addition to δ-unsubstituted β-ketoesters and glycine imines.*

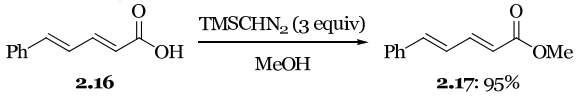


In all of these methodologies the excellent regioselectivity is associated with specific structural features of the substrate. Enantioselective conjugate addition of nucleophiles to particularly challenging acyclic dienones or dienoates nonsubstituted at the β- and monosubstituted at the δ-position has not been reported yet. The challenges to achieve regio- and enantioselective 1,6-addition to these kind of substrates are in particular evident from the work of Hayashi et al.;[12] using acyclic **2.7** for the asymmetric 1,6-addition of PhZnCl low regio- (70%) and enantioselectivity (77%) was obtained (Scheme 2.2). In particular the addition of simple alkyl groups to dienoates is highly warranted due to the synthetic versatility of the chiral multifunctional building blocks obtained. Herein, we report the first Cu-catalyzed ACA of simple alkyl Grignard reagents to linear δ-substituted-2,4-dienoates.

2.2 Synthesis of α,β,γ,δ-bisunsaturated Michael acceptors

Large conjugated unsaturated systems can be found in a variety of natural products. For example multiple conjugated alkenes are incorporated in the structure of vitamin A1 (retinol)[15] and dictyostatin,[16] a compound active against a variety of human cancer cell lines. Often these products are prepared via

Scheme 2.5. *Preparation of α,β,γ,δ-bisunsaturated esters via esterification.*



2.16 **2.17**: 95%

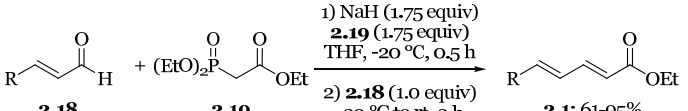
bisunsaturated esters. Hence there are several synthetic routes towards α,β,γ,δ-bisunsaturated Michael acceptors.

In a first route the required products are prepared by esterification of commercially available α,β,γ,δ-bisunsaturated acids. For example, conversion of **2.16** using $TMSCHN_2$[17] gave **2.17** in excellent yield (Scheme 2.5).

A second route towards dienoates employs the Horner-Wadsworth-Emmons (HWE) reaction.[18] In this reaction monounsaturated aldehydes can be reacted with deprotonated **2.19**. The desired products **2.1** are obtained in good to excellent yields (Scheme 2.6).

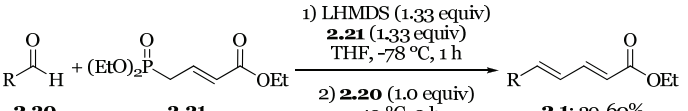
Finally, using the extended HWE reagent **2.21**, saturated aldehydes can be converted to bisunsaturated esters.[19] As depicted in Scheme 2.7 the synthesis of **2.1** was performed with good yields. However, the separation of the 2*E*,4*E*-product **2.1** from the 2*E*,4*Z*-product is often troublesome and gave the pure 2*E*,4*E*-product **2.1** in mediocre yields.

Scheme 2.6. *Synthesis of α,β,γ,δ-bisunsaturated esters via HWE reaction.*



2.18 **2.19** **2.1**: 61-95% for R=Et, *i*Pr, *n*Bu

Scheme 2.7. *Synthesis of α,β,γ,δ-bisunsaturated esters using HWE reagent* ***2.21****.*

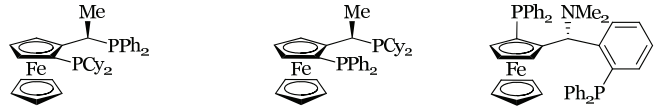


2.20 **2.21** **2.1**: 39-60% for R=*i*Bu, CH_2OBn, $CH_2OTBDPS$, CH_2Bn

2.3 Optimization of the asymmetric 1,6-addition

Recently, an extensive study on the mechanism of the 1,4-ACA of Grignard reagents was reported from our laboratory.[20] Noting the proposed mechanistic similarities between the 1,4-ACA and 1,6-CA[21,i] we decided to further expand this catalytic system[22] towards 1,6-ACA. As an initial model reaction the

[i] For further discussion see chapter 3.

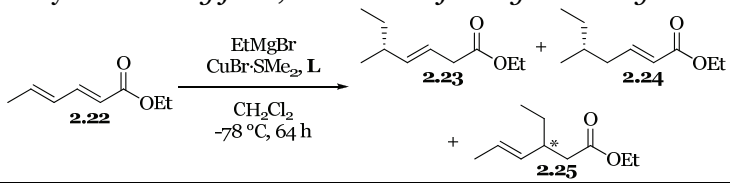


(*R*,*S*)-(-)-**L2.4**, reversed JosiPhos (*R*,*S*)-(-)-**L2.5**, JosiPhos (*R*,*R*)-(-)-**L2.6**, TaniaPhos

Figure 2.1. *Chiral ferrocenyl based phosphines used in ACA of Grignard reagents.*
Used abbreviation: Cy=cyclohexyl.

addition of EtMgBr to commercially available ethyl sorbate **2.22** was chosen. Employing the reversed JosiPhos ligand (+)-**L2.4** (Figure 2.1, (−)-**L2.4** shown) at −78 °C the β,γ-unsaturated 1,6-addition product **2.23** was obtained with excellent regio- and enantioselectivity (Table 2.1, entry 1 and 2). Remarkably, only a trace (<2%) of 1,4-addition product **2.25** and no 1,2-addition product were detected by GC-analysis. Furthermore, we did not obtain any of the α,β-unsaturated 1,6-addition product **2.24**; because in situ quenching of the magnesium bromide dienolate by ethanol gives the kinetic β,γ-unsaturated ester product **2.23** (Scheme 2.8).

Table 2.1. Catalyst *screening for 1,6-addition of EtMgBr to ethyl sorbate (**2.22**).*[a]



entry	ligand	conversion (%)	**2.23**:**2.25**[b]	ee[b,c] (%)
1	(+)-**L2.4**	>99	98:2	95 (*R*)
2[d]	(−)-**L2.4**	>99	99:1	95 (*S*)
3	(−)-**L2.5**	~80	-	-
4	(−)-**L2.6**	~35	-	-
5	-	>99	34:66	0

[a] Conditions: a solution of **2.22** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), ligand (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **2.22**). [b] Ratio **2.23**:**2.25** and ee's were determined by chiral GC. [c] Absolute configuration of **2.23** was determined by conversion to known compound (see experimental section). [d] Reaction was performed at −70 °C for 16 h.

Scheme 2.8. *Trapping of dienolate **2.26** gives the β,γ-unsaturated ester product.*

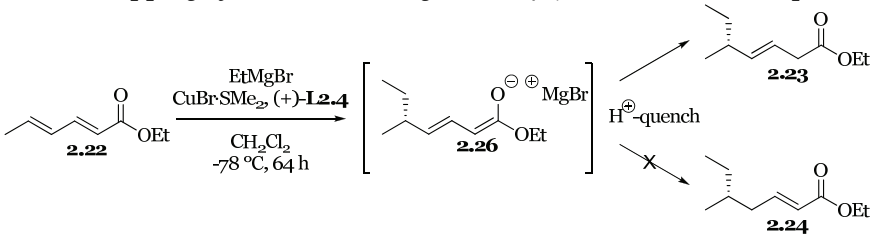
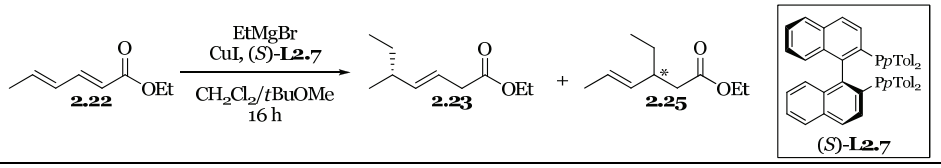


Table 2.2. *Screening for the 1,6-addition of EtMgBr to ethyl sorbate (**2.22**) using Tol-BINAP ((S)-**L2.7**) as ligand.*[a]



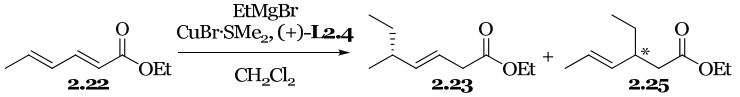
entry	temperature (°C)	conversion (%)	**2.23**:**2.25**[b]	ee **2.23**[b,c] (%)	ee **2.25**[b] (%)
1	−40	>95	49:51	nd	~0
2	−50	>95	48:52	nd	~0
3	−60	>95	65:35	nd	~0
4	−70	>95	73:33	29 (*S*)	~0
5	−78	~10	nd	nd	nd

[a] Conditions: a solution of **2.22** in *t*BuOMe was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), **L2.7** (7.5 mol%) and CuI (5 mol%) in CH_2Cl_2 and *t*BuOMe (1:2; total 0.2 M in **2.22**). [b] Ratio **2.23**:**2.25** and ee's were determined by chiral GC. [c] Absolute configuration of **2.23** was determined by conversion to a known compound (see experimental section).

The asymmetric 1,6-addition is remarkably sensitive to the structure of the catalyst. The use of either JosiPhos (−)-**L2.5** or TaniaPhos (−)-**L2.6** at −78 °C led to less than 5% yield[ii] in 64 h (Table 2.1, previous page, entry 3 and 4). In contrast, the use of a catalytic amount of non-ligated copper at −78 °C led to formation of a mixture of regioisomers with a preference for the 1,4-addition product **2.25** (entry 5). Finally, using the Tol-BINAP ligand (**L2.7**)[23] at an optimum temperature **2.23** could be obtained with a modest regioselectivity and low ee (Table 2.2).[24]

Since the reaction using (+)-**L2.4** was found to be slow at −78 °C the influence of the temperature was investigated. Increasing the temperature of the reaction mixture up to −60 °C allowed shorter reaction times (4 h) without loss of regio- or stereoselectivity (Table 2.3, entry 1 vs. 2). However, the use of higher temperatures led to gradual loss of both regio- and stereoselectivity (entry 3 and 4).

Table 2.3. *Temperature optimization for 1,6-addition of EtMgBr to **2.22**.*[a]



entry	temperature (°C)	reaction time (h)	conversion (%)	**2.23**:**2.25**[b]	ee[b,c] (%)
1	−78	64	>99	98:2	95 (*R*)
2	−60	4	>99	99:1	95 (*R*)
3	−55	3	>99	98:2	92 (*R*)
4	−40	2.5	>99	77:23	67 (*R*)

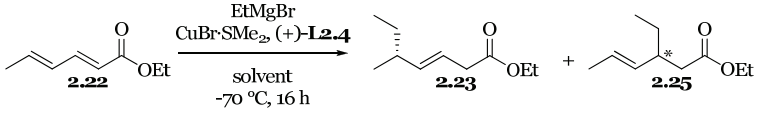
[a] Conditions: a solution of **2.22** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**L2.4** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **2.22**). [b] Ratio **2.23**:**2.25** and ee's were determined by chiral GC. [c] Absolute configuration was determined by conversion to known compound (see experimental section).

[ii] Mainly degradation of starting material was observed.

Screening of solvents identified CH_2Cl_2 as the solvent which results in the highest regio- and enantioselectivity (Table 2.4, entry 1). The use of *t*BuOMe or toluene as solvent also yielded the 1,6-addition products in good regioselectivity and ee (entry 2 and 3). Remarkably, in pure Et_2O only 10% yield of **2.23** was obtained (entry 4).

Finally, to demonstrate the synthetic potential of this methodology we performed a 0.5 g-scale reaction with only 2 mol% of catalyst which gave **2.23** in good yield (77%) with excellent regio- (99:1) and enantioselectivity (95%).

Table 2.4. *Solvent screening for the 1,6-addition of EtMgBr to ethyl sorbate (**2.22**).*[a]



entry	solvent	conversion (%)	yield (%)	**2.23**:**2.25**[b]	ee[b,c] (%)
1	CH_2Cl_2	>95	84	98:2	95 (*R*)
2	*t*BuOMe	>95	nd[d]	99:1	94 (*R*)
3	toluene	>95	nd[d]	98:2	90 (*R*)
4	Et_2O	>95	<10	77:23	nd

[a] Conditions: a solution of **2.22** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**L2.4** (5.25 mol%) and CuBr·SMe_2 (5 mol%) in a solvent (0.2 M in **2.22**). [b] Ratio **2.23**:**2.25** and ee's were determined by chiral GC. [c] Absolute configuration of **2.23** was determined by conversion to known compound (see experimental section). [d] Yields are similar to the reaction in CH_2Cl_2.

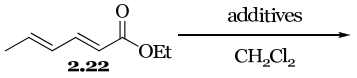
2.4 Stability of ethyl sorbate under reaction conditions

To obtain good yields for the enantioselective 1,6-addition, a slow addition protocol of the substrate to the reaction mixture was used (77% yield for dropwise addition vs. 84% yield for slow addition using a syringe pump). The reason for the increase in yield using a slow addition mode is not obvious since for both protocols no side products are detected by NMR-analysis or GC-MS analysis of the crude reaction mixture. It is conceivable that **2.22** polymerizes[iii] under the reaction conditions as sorbates are frequently used as substrates for radical[25] or anionic[26] polymerization.

To test this hypothesis, the stability of **2.22** under the reaction conditions was examined employing dodecane as internal standard (Table 2.5). Stirring a solution of **2.22** in CH_2Cl_2 at rt for 16 h already results in 20-25% degradation (entry 1), presumably **2.22** is polymerized since no side-products are detected by GC-MS. At the temperature of the reaction (−70 °C), ethyl sorbate is stable even in the presence of CuBr•SMe_2, CuBr•SMe_2 and **L2.4** or a Grignard reagent (entry 2-5). However, when a combination of CuBr•SMe_2 and Grignard reagent is used no **2.22** is recovered (entry 6 and 7). Again the formation of any conjugate addition products or any other GC-MS detectable side-products was not observed.

[iii] The presumed polymerized products have not been characterized.

Table 2.5. *Stability of ethyl sorbate.*[a]



2.22

entry	reaction time (h)	temperature (°C)	additives	**2.22** recovered (%)[b]
1	16	rt	-	76/78[c]
2	64	−70	-	94
3	16	−70	$CuBr{\bullet}SMe_2$	95
4	16	−70	$CuBr{\bullet}SMe_2$ + **L2.4**	100
5	64	−70	*i*PrMgBr	94
6	16	−70	$CuBr{\bullet}SMe_2$ + *i*PrMgBr	0
7	16	−70	$CuBr{\bullet}SMe_2$ + EtMgBr	0

[a] Conditions: **2.22** in CH_2Cl_2 (0.2 M in **2.22**) and if used Grignard reagent (3.0 M in Et_2O, 2.0 equiv), **L2.4** (5.25 mol%) and/or $CuBr{\cdot}SMe_2$ (5 mol%). [b] No 1,6-, 1,4- or 1,2-addition products were observed by GC-MS. [c] Entry was performed in duplo.

The conversion of **2.22** to unknown products under the conditions given in entry 6 and 7 suggests that the combination of Grignard reagent and Cu allows the formation of radical species, even at low temperature, and starts the radical polymerization of ethyl sorbate.[iv] The slow addition protocol might keep the concentration of **2.22** low enough to decrease the degree of polymerization and therefore provide the product in better yields.

2.5 Grignard reagent and substrate scope for the asymmetric 1,6-addition to linear dienoates

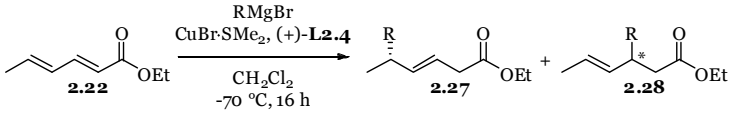
After optimization of the reaction conditions and having achieved excellent regio- and enantioselectivity, the scope of 1,6-ACA with respect to addition of different Grignard reagents was examined.[v] Grignard reagents possessing longer alkyl chains (Table 2.6, entry 2) and a homoallylic Grignard (entry 3) also gave excellent ee's and regioselectivity. Addition of the sterically hindered Grignard *i*PrMgBr yields a respectable ee (72%) (entry 4). However, addition of other sterically hindered and aryl Grignard reagents resulted in very low conversion even at −60 °C in 16 h (entry 5 to 7).

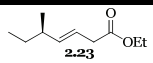
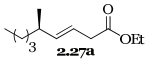
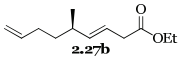
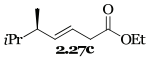
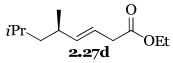
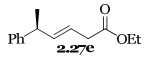
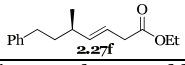
To further examine the scope of the 1,6-ACA with respect to δ-substitution in the substrate we tested our optimal conditions for several bisunsaturated esters. Linear aliphatic chains at the δ-position provided similar high levels of selectivity (Table 2.7, entry 1, 2). Reversing the order of the alkyl moiety in the substrate and the Grignard reagent provides access to both enantiomers of **2.30a** using only a single configuration of the catalyst (Scheme 2.10, next page). Bulky substituents at the ε-position (entry 3) caused a drop in regio- and enantioselectivity. In addition to the anticipated β,γ-unsaturated product **2.30c** the α,β-unsaturated product **2.31c** was obtained. Excellent control of regio- and stereoselectivity was achieved again

[iv] However, initial attempts to improve the yield of the 1,6-ACA of *i*PrMgBr to **2.22** by trapping of the presumed radicals employing either styrene or benzoquinone were unsuccessful.

[v] Freshly prepared Grignard reagents should be used to obtain good yields.

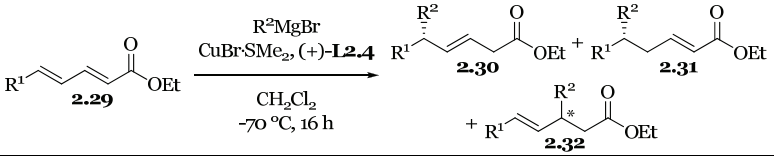
Table 2.6. *Asymmetric 1,6-addition of several Grignard reagents to* **2.22**.[a]

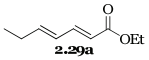
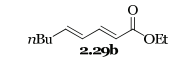
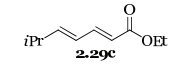
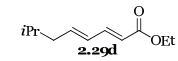
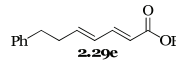
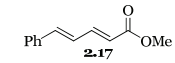
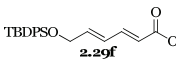
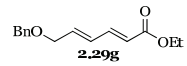


entry	R	product	yield (%)	**2.27**:**2.28**[b]	ee[b,c] (%)
1	Et	 **2.23**	84	98:2	95 (*R*)
2	*n*Bu	 **2.27a**	85	99:1	97 (–)
3	but-3-enyl	 **2.27b**	57	97:3	92 (–)
4	*i*Pr	 **2.27c**	54	99:1	72 (–)
5	*i*Bu	 **2.27d**	<5[d]	-	-
6	Ph	 **2.27e**	<5[d]	-	-
7	$BnCH_2$	 **2.27f**	<5[d]	-	-

[a] Conditions: a solution of **2.22** in CH_2Cl_2 was added to a solution of RMgBr (1.5-3.0 M in Et_2O, 2.0 equiv), (+)-**L2.4** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **2.22**). [b] Ratio **2.27**:**2.28** and ee's were determined by chiral GC. [c] Absolute configuration was determined by conversion to known compound (see paragraph 2.11). [d] Conversion (presumably to polymerized products) was ~35%.

Table 2.7. *Enantioselective 1,6-addition of Grignard reagents to several dienoates.*[a]

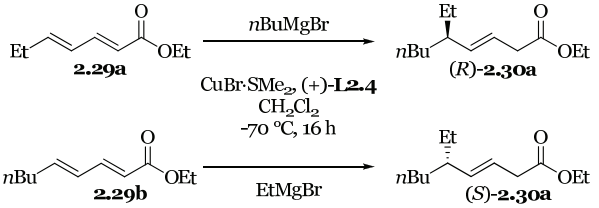


entry	Substrate	R^2	product	yield (%)	**2.30**:**2.32**[b]	ee[b] (%)
1	 **2.29a**	*n*Bu	**2.30a**	88	99:1	96 (–)
2	 **2.29b**	Et	**2.30a**	80	99:1	93 (+)
3	 **2.29c**	Et	**2.30c** + **2.31c**[c]	82	96:4	79 (–)
4	 **2.29d**	Et	**2.30d**	77	98:2	93 (+)
5	 **2.29e**	Et	**2.30e**	73	98:2	90 (+)
6	 **2.17**	Et	**-**[d]	-	-	-
7	 **2.29f**	Et	**2.30f**	82	96:4	73 (–)
8	 **2.29g**	Et	**2.30g**	69	>95:5[e]	90 (–)

[a] For conditions see Table 2.6. [b] Ratio **2.30**:**2.32** and ee's were determined by chiral GC or HPLC. [c] **2.31c** is present in varying amounts (35-50%) [d] Complex mixture of products obtained. [e] Ratio **2.30g**: **2.32g** was determined by ^{1}H-NMR.

when the bulky substituents are separated by an additional CH_2 spacer from the dienoate unit (entry 4). High ee was obtained as well for the substrate functionalized with a phenyl moiety (entry 5). However, the reaction of the δ-substituted substrate **2.17** gave none of the intended product but a complex mixture of products (entry 6). Finally, functionalization by a bulky TBDPS protected hydroxyl at the ε-position caused a drop in regio- and enantioselectivity (entry 7). Replacing the TBDPS protective group by the less sterically demanding Bn group provided high regio- and stereocontrol again (entry 8).

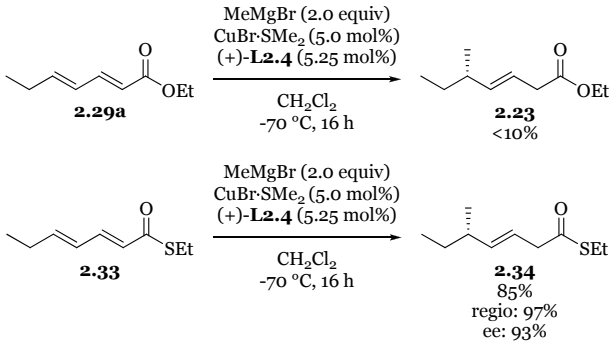
Scheme 2.10. *Synthesis of (S)- and (R)-**2.30a** with a single configuration of **L2.4**.*



2.6 Grignard reagent and substrate scope for the asymmetric 1,6-addition to linear dienothioates and dienones

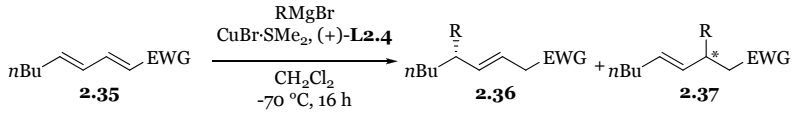
Since chiral Me-substituted alkyl chains are abundant in natural products[27] the ACA of MeMgBr comprises particularly important synthetic methodology.[22d,28] In earlier work, Feringa and co-workers used α,β-unsaturated thioesters to overcome the intrinsic low reactivity of ester substrates to MeMgBr. Thioesters are more reactive in ACA because of the reduced orbital overlap of the sulfur 3p-orbitals with the π-system of the carbon-oxygen double bond compared to the 2p-orbitals of the oxygen of carboxylic esters with the carbon-oxygen π-system.[29] Also for 1,6-ACA, this tuning of reactivity was needed to allow enantioselective addition of MeMgBr. Ester substrate **2.29a** gave as expected a low yield of product **2.23** (Scheme 2.11); however the use of thioester **2.33** instead yielded the anticipated product **2.34** in high yield and excellent regio- and enantioselectivity.

Scheme 2.11. *Enantioselective 1,6-addition of MeMgBr to ester substrate **2.29a** and thioester substrate **2.33**.*



The scope of the 1,6-ACA to these more reactive Michael acceptors was examined by addition of several Grignard reagents to (2*E*,4*E*)-S-ethyl nona-2,4-dienethioate[22d] and (3*E*,5*E*)-deca-3,5-dien-2-one[30] (Table 2.8). For the addition of EtMgBr,[vi] a decrease in enantioselectivity compared to the selectivity for the addition of MeMgBr was found (entry 3 vs. entry 2). Interestingly, this drop of enantioselectivity cannot be attributed to a blank reaction (entry 1). For the addition of Grignard reagents to dienones a low regio- and enantioselectivity was observed (entry 5 and 7). Again, for the addition of MeMgBr the drop in enantio- and regioselectivity cannot be explained by a blank reaction (entry 4). For the addition of EtMgBr the drop of regioselectivity might be partly explained by a competing non-catalyzed 1,4-addition of the substrate with the Grignard reagent (entry 6). However, presumably the catalyzed reaction is much faster than the non-catalyzed.[vii]

Table 2.8. *Scope of the 1,6-ACA to dienothioates and dienones.*[a]



entry	EWG	R	yield (%)	**2.36**:**2.37**[b]	ee[b] (%)
1[c]	COSEt	Et	<10%[d]	-	-
2	COSEt	Me	93%	98:2	89%
3	COSEt	Et	58%	>95:5[e]	~40%
4[c]	COMe	Me	83%[d]	-[f]	-
5	COMe	Me	54%	63:37	66%
6[c]	COMe	Et	>95%[d]	<5:95[g]	-
7	COMe	Et	~60%	63:37	~30%

[a] Conditions: **2.35** was added to a solution of RMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**L2.4** (5.25 mol%) and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **2.35**). [b] Ratio **2.36**:**2.37** and ee's were determined by chiral GC. [c] Ligand and copper were omitted. [d] Conversion. [e] Determined by NMR. [f] 1,2-addition product obtained (83%). [g] 1,2-addition product obtained (39%).

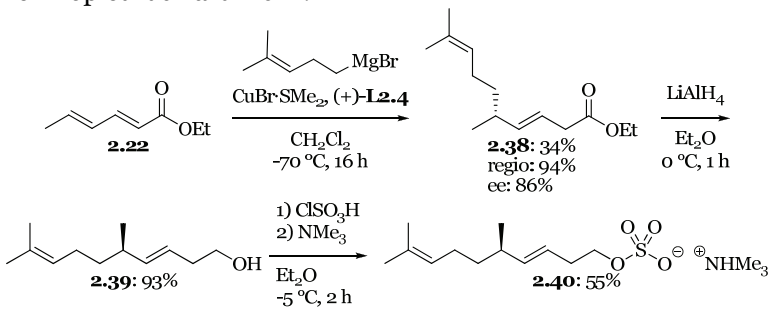
[vi] Preliminary results gave a similar enantioselectivity and regioselectivity for the Cu-catalyzed 1,6-ACA using JosiPhos as ligand (in contrast to the use of the same ligand for the 1,6-ACA to α,β,γ,δ-bisunsaturated oxoesters reported in paragraph 2.3)

[vii] Since the 1,2-addition product is absent in the reaction leading to the results described in entry 7.

2.7 A short synthesis of a natural occurring sulphated alkene

To illustrate the potential of the novel 1,6-ACA, a short total synthesis of a sulphated alkene, isolated from the sea-urchin *Temnopleurus hardwickii*,[31] was performed. As shown in Scheme 2.12 this synthesis features a 0.5 g scale asymmetric 1,6-addition of (4-methylpent-3-en-1-yl)magnesium bromide on ethyl sorbate (**2.22**) with high enantioselectivity, followed by $LiAlH_4$ reduction of the ester and sulfation of the alcohol to provide **2.40** in good yield and stereoselectivity (3 steps, 17% overall yield, 86% ee).

Scheme 2.12. *A short total synthesis of a sulphated alkene (**2.40**) isolated from the sea-urchin* Temnopleurus hardwickii.[a]



[a] Conditions: **2.38**: **2.22** (1.0 equiv, 0.5 g scale), $Me_2CCH(CH_2)_2MgBr$ (1.2 equiv), $CuBr{\bullet}SMe_2$ (2 mol%), **L2.4** (2.2 mol%), CH_2Cl_2 (5 mL/mmol **2.22**); **2.39**: **2.38** (1.0 equiv, 150 mg scale), $LiAlH_4$ (2.2 equiv), Et_2O (10 mL/mmol **2.38**); **2.40**: 1) **2.39** (1.0 equiv, 60 mg scale), $ClSO_3H$ (1.0 equiv), Et_2O (1.5 mL/mmol **2.39**); 2) NMe_3 (excess).

2.8 Conclusions

In conclusion, a highly enantioselective 1,6-ACA (up to 97% ee) to α,β,γ,δ-unsaturated esters was developed. This is the first example of a 1,6-ACA for which regioselectivity is primarily dictated by the catalyst and the first example of asymmetric 1,6-CA of Grignard reagents. The 1,6-ACA provides valuable multifunctional building blocks. Further studies have been performed to examine the scope of this methodology, as well as to investigate the reaction mechanism (see chapter 3).

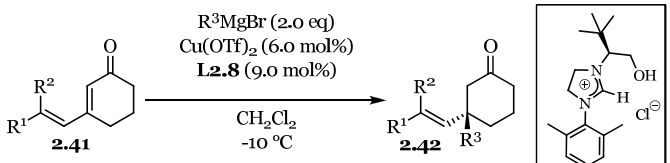
2.9 Perspective and outlook

The asymmetric 1,6-addition is a good example of how asymmetric catalysis can control chemo-, as well as, regio- and enantioselectivity. The enantioselectivity observed for the 1,6-ACA is similar to the enantioselectivities observed for the 1,4-ACA.[22c] The 1,6-ACA products incorporate several functionalities which can easily be modified using follow-up chemistry. Highly desirable transformations with the 1,6-addition products would be the isomerisation of the β,γ-unsaturated ester to the α,β-unsaturated ester and subsequent CA reactions (see chapter 4), as well as, asymmetric *cis*-dihydroxylation[32] or epoxidation[33] to form propionate units (see chapter 5).[34] Finally, the intermediate dienolate provides extra possibilities for interaction with transition metals and thus possibly for catalyzed electrophilic trapping reactions.[35]

However, the developed method also has some limitations as synthetic methodology. First of all, the 2 mol% catalyst loading required to obtain the products with good ee is relatively high, especially seen from a preparative perspective. Furthermore, the instability of the starting materials is a drawback. Finally, the somewhat narrow Grignard scope of the methodology is a limitation.

In addition to a synthetic methodology, the 1,6-ACA can be exploited as a mechanistic tool for asymmetric Cu-catalyzed reactions. Since the 1,6-ACA is much slower (16 h, −70 °C) compared to the related 1,4-ACA (2 h, −78 °C) it might allow the identification of catalytic intermediates (see further chapter 3).

Scheme 2.13. *Selective 1,4-ACA on selected cyclic dienones.*



R¹: Me, cyclohexyl, *n*Pr; R²: H, Me; R³: Et, *n*Bu, but-3-enyl;
yield: 44-67%; regio: 90%->98%; ee: 92-99%; 6 examples

R¹: Me; R²: H; R³: *i*Pr, *i*Bu;
yield: 25-39%; regio: 12%-30%; ee: 95-99%

Having achieved selective 1,6-addition another challenge is selective 1,4-addition on bisunsaturated Michael acceptors. In 2008, after the completion of this work, Alexakis and co-workers[36] elegantly showed that an NHC-ligand (**L2.8**) can be used to perform 1,4-ACA on selected cyclic dienones in high selectivity (Scheme 2.13). However, the 1,4-ACA on linear Michael acceptors, monosubstituted at the β- and δ-position, remains a challenge.

2.10 Acknowledgement

D. Font is acknowledged for the identification of reversed JosiPhos as suitable ligand for regioselective 1,6-addition. Dr. S. R. Harutyunyan is acknowledged for fruitful discussions.

2.11 Experimental section

General procedures:
All reactions were conducted under a N_2 atmosphere using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere prior to use. CuBr•SMe_2 was purchased from Sigma-Aldrich. (+)-(*S*,*R*)-reversed JosiPhos was generously donated by Solvias. (−)-(*R*,*S*)-reversed JosiPhos was purchased from Sigma-Aldrich. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, *i*BuMgBr and PhMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et_2O following standard procedures. Grignard reagents were titrated using *s*BuOH and small amounts of 1,10-phenanthroline before use.
$RuCl_3$•$3H_2O$, DIBAL-H (1.0 M solution in CH_2Cl_2), $LiAlH_4$ and NMe_3 were purchased from Sigma-Aldrich. $NaIO_4$ was purchased from Merck. Et_2O was distilled from benzophenone-ketyl under a N_2 atmosphere prior to use. Chlorosulfonic acid was purchased from Sigma-Aldrich and distilled under a N_2 atmosphere prior to use.
Thin-layer chromatography (TLC) was performed on commercial Kieselgel $60F_{254}$ silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by capillary GC analysis (HP6890, CP-Chiralsil-Dex-CB [25 m x 0.25 mm]; Shimadzu GC-17A, CP-Chiraldex-B-PM [30 m x 0.25 mm]) using flame ionization detection or HPLC analysis ((*R*,*R*)-Whelk-01, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 205 nm; chiralcel OD-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 205 nm) in comparison to authentic samples of racemates of 1,6- and 1,4-addition products. Optical rotations were measured in CH_2Cl_2 on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL), a trace contamination (~2%) of 1,4-addition product was present; which in all cases was inseparable by column chromotography. Absolute configurations were determined by comparison of either retention times on chiral GC-spectra (2-methylbutanoic acid) or optical rotation of compounds previously published. ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ= 7.26 for hydrogen atoms, δ= 77.0 for carbon atoms). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a AEI-MS-902 mass spectrometer by EI (70 ev) measurements.
For spectra see supporting information of the paper mentioned on page 55.

General procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β,γ,δ-bisunsaturated carboxylic acids (A):
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, the substrate (1 equiv) was dissolved in anhydrous MeOH (2 mL/mmol substrate). $TMSCHN_2$ (3 equiv [unoptimized]) was added dropwise and the mixture was stirred for 3 h. Then a saturated aq solution of $NaHCO_3$ (2 mL/mmol substrate) was added and the mixture was extracted with Et_2O (3x 2 mL/mmol substrate). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2*E*,4*E*-methyl 5-phenylpenta-2,4-dienoate (**2.17**) was prepared via general procedure A in 95% isolated yield (1.0 g/5.7 mmol scale).
White solid; data were in accordance with those given in ref 37.

General procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadworths-Emmons reaction (B):[18]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, NaH (1.75 equiv) was vigorously stirred in anhydrous THF (1 mL/mmol aldehyde) and cooled to −20 °C. Triethyl phosphonoacetate (neat, 1.75 equiv) was added dropwise and the mixture was stirred for 30 min. Subsequently, the aldehyde (1 equiv) dissolved in anhydrous THF (0.1 mL/mmol aldehyde) was added dropwise. After addition, the solution was stirred for 20 min at −20 °C and was subsequently stirred at rt for 30 min. The reaction mixture was diluted with Et_2O (2 mmol/mmol aldehyde) and the solution was subsequently washed with NH_4Cl (saturated aq solution, 2 mL/mmol aldehyde), Na_2CO_3 (saturated aq solution, 2 mL/mmol aldehyde) and brine (2 mL/mmol aldehyde). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2E,4E-ethyl hepta-2,4-dienoate (**2.29a**) was prepared via general procedure B in 61% isolated yield (0.86 g/10.22 mmol scale).
Colorless oil; data were in accordance with those given in ref 18.

2E,4E-ethyl nona-2,4-dienoate (**2.29b**) was prepared via general procedure B in 91% isolated yield (0.42 g/3.74 mmol scale).
Colorless oil; ^{1}H NMR δ 7.24-7.15 (m, 1H), 6.15-6.00 (m, 2H), 5.71 (d, *J*= 15.3 Hz, 1H), 4.13 (qd, *J*= 7.1 Hz, 1.1 Hz, 2H), 2.10 (q, *J*= 6.6 Hz, 2H) , 1.27 (m, 7H), 0.84 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 167.0 (C), 144.8 (CH), 144.4 (CH), 128.2 (CH), 119.0 (CH), 59.9 (CH_2), 32.5 (CH_2), 30.7 (CH_2), 22.1 (CH_2), 14.1 (CH_3), 13.7 (CH_3); MS *m/z* 182 (M^+, 68), 125 (M-*n*Bu, 100), 97 (C_7H_{13}, 48); HRMS calcd. for $C_{11}H_{18}O_2$ 182.1307, found 182.1316.

2E,4E-ethyl 6-methylhepta-2,4-dienoate (**2.29c**) was prepared via general procedure B in 95% isolated yield (0.42 g/4.30 mmol scale).
Colorless oil; data were in accordance with those given in ref 38.

General procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from alkyl aldehydes via Horner-Wadworths-Emmons reaction with *E*-triethylphosphonocrotonate[viii] (C):[19]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, *E*-triethylphosphonocrotonate (1.3 equiv) was dissolved in anhydrous THF (1 mL/mmol aldehyde) and cooled to −78 °C. LHMDS (1.0 M solution in THF, 1.3 equiv) was added dropwise and the mixture was stirred for 2 h. Then, aldehyde (1 equiv) dissolved in anhydrous THF (0.5 mL/mmol substrate) was added dropwise. After addition, the solution was stirred at −40 °C for 4 h. A solution of NH_4Cl (1 M aq solution, 1 mL) was added and the mixture extracted with Et_2O (3x 2 mL). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2E,4E-ethyl 7-methylocta-2,4-dienoate (**2.29d**) was prepared via general procedure C in 44% isolated yield (0.65 g/7.5 mmol scale).
Colorless oil; data were in accordance with those given in ref 18. MS *m/z* 182 (M^+, 100), 127 (88), 125 (M-*i*Bu, 91), 67 (C_5H_7, 94); HRMS calcd. for $C_{11}H_{18}O_2$ 182.1307, found 182.1311.

2E,4E-ethyl 7-phenylhepta-2,4-dienoate (**2.29e**) was prepared via general procedure C in 32% isolated yield (1.09 g/7.5 mmol scale).
Colorless oil; ^{1}H NMR δ 7.34-7.14 (m, 6H), 6.27-6.08 (m, 2H), 5.79 (d, *J*= 15.1 Hz, 1H), 4.20 (q, *J*= 7.1 Hz, 2H), 2.75 (t, *J*= 8.0 Hz, 2H), 2.56-2.43 (m, 2H), 1.29 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 167.2 (C),

[viii] Triethylphosphonocrotonate was purchased from Aldrich (90% technical grade) and purified by column chromatography (gradient 25:75 to 1:0 Et_2O:pentane) to give pure *E*-triethylphosphonocrotonate.

144.8 (CH), 143.1 (CH), 141.1 (C), 128.9 (CH), 128.4 (CH), 128.4 (CH), 126.0 (CH), 119.6 (CH), 60.2 (CH_2), 35.1 (CH_2), 34.7 (CH_2), 14.3 (CH_3); MS *m/z* 230 (M^+, 10), 91 (C_7H_7, 100); HRMS calcd. for $C_{15}H_{18}O_2$ 230.1307, found 230.1308.

2E,4E-ethyl 6-(*tert* butyldiphenylsilyloxy)hexa-2,4-dienoate (**2.29f**) was prepared via general procedure C in 28% isolated yield (0.76 g/2.6 mmol scale).
Colorless oil; ^{1}H NMR δ 7.70-7.65 (m, 4H), 7.48-7.36 (m, 6H), 7.31 (dd, *J*= 15.3 Hz, 11.2 Hz, 1H), 6.59-6.42 (m, 1H), 6.16 (dt, *J*= 15.2 Hz, 4.2 Hz, 1H), 5.89 (d, *J*= 15.2 Hz, 1H), 4.34-4.30 (m, 2H), 4.22 (q, *J*= 7.1 Hz, 2H), 1.31 (t, *J*= 7.1 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR δ 166.9 (C), 143.9 (CH), 141.2 (CH), 135.3 (CH), 133.1 (C), 129.7 (CH), 127.7 (CH), 126.8 (CH), 120.8 (CH), 63.5 (CH_2), 60.1 (CH_2), 26.7 (CH_3), 19.1 (C), 14.2 (CH_3); MS *m/z* 394 (M^+, 27), 337 (M-*t*Bu, 100), 227 (TBDPSOEt-*t*Bu, 41), 199 (TBDPSOH-*t*Bu, 66); HRMS calcd. for $C_{24}H_{30}O_3Si$ 394.1964, found 394.1982.

2E,4E-ethyl 6-(benzyloxy)hexa-2,4-dienoate (**2.29g**) was prepared via general procedure C in 20% isolated yield (1.09 g/6.7 mmol scale).
Colorless oil; ^{1}H NMR δ 7.45-7.27 (m, 6H), 6.42 (m, 1H), 6.18 (dt, *J*= 14.8 Hz, 5.0 Hz, 1H), 5.89 (dd, *J*= 15.4 Hz, 0.5 Hz, 1H), 4.54 (s, 2H), 4.21 (q, *J*= 7.1 Hz, 2H), 4.13 (d, *J*= 5.3 Hz, 2H), 1.29 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 166.9 (C), 143.6 (CH), 138.5 (CH), 137.8 (C), 129.1 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 121.4 (CH), 72.5 (CH_2), 69.5 (CH_2), 60.3 (CH_2), 14.2 (CH_3); MS *m/z* 246 (M^+, 1), 91 (C_7H_7, 100); HRMS calcd. for $C_{15}H_{18}O_3$ 246.1256, found 246.1256.

General procedure for the synthesis of α,β,γ,δ-bisunsaturated thioesters from α,β-unsaturated aldehydes via Wittig reaction (D):
This procedure was described for the reaction of aldehydes with $Ph_3PCHCOSEt$ in ref 22d (procedure D, 24 h reaction time)

2E,4E-S-ethyl hepta-2,4-dienethioate (**2.33**) was prepared via general procedure D in 14% isolated yield (0.86 g/1.02 mmol scale).
Colorless oil; ^{1}H NMR δ 7.17 (dd, *J*= 15.2 Hz, 10.6 Hz, 1H), 6.22 (dt, *J*= 15.1 Hz, 6.4 Hz, 1H), 6.15-6.01 (m, 2H), 2.93 (q, *J*= 7.4 Hz, 2H), 2.23-2.12 (m, 2H), 1.26 (t, *J*= 7.4 Hz, 3H), 1.03 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR δ 190.1 (C), 147.5 (CH), 140.9 (CH), 127.2 (CH), 126.4 (CH), 26.2 (CH_2), 23.1 (CH_2), 14.8 (CH_3), 12.8 (CH_3); MS *m/z* 170 (M^+, 16), 109 (M-SEt, 100), 81 (M-COSEt, 66); HRMS calcd. for $C_9H_{14}OS$ 170.0765, found 170.0773.

2*E*,4*E*-S-ethyl nona-2,4-dienethioate (**2.35**, EWG=COSEt) was prepared via general procedure D in 61% isolated yield (5.43 g/14.9 mmol scale).
Colorless oil; ^{1}H NMR δ 7.16 (dd, *J*= 15.2 Hz, 10.1 Hz, 1H), 6.22-6.09 (m, 2H), 6.05 (d, *J*= 15.2 Hz, 1H), 2.93 (*J*= 7.4 Hz, 2H), 2.16 (dd, *J*= 13.9 Hz, 6.7 Hz, 2H), 1.39 (dt, *J*= 14.4 Hz, 7.2 Hz, 2H), 1.34-1.29 (m, 2H), 1.26 (td, *J*= 7.4 Hz, 0.5 Hz, 3H), 0.88 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR δ 190.3 (C), 146.6 (CH), 141.1 (CH), 128.4 (CH), 126.6 (CH), 33.1 (CH_2), 31.0 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 15.1 (CH_3), 14.1 (CH_3); MS *m/z* 198 (M^+, 14), 137 (M-SEt, 100), 81 (C_5H_5O, 39); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1083.

3*E*,5*E*-deca-3,5-dien-2-one (**2.35**, EWG=COMe) was prepared via general procedure B using NaH (2.7 equiv) and diethyl (2-oxopropyl)phosphonate as HWE reagent (3.0 equiv) in THF (10 mL/mmol substrate + addition of substrate in additional 2 mL/mmol substrate) in 65% isolated yield (0.86 g/7.64 mmol scale).
Colorless oil; data were in accordance with those given in ref 39.

General procedure for the enantioselective 1,6-conjugate addition (E):
(exemplified for the addition of EtMgBr to **2.22**)
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuBr•SMe_2 (5.14 mg, 25 µmol, 5.0 mol%) and (*R,S*)-reversed Josiphos (15.46 mg, 26 µmol, 5.25 mol%) were dissolved in anhydrous CH_2Cl_2 (2 mL). After 5 min stirring at rt the mixture was cooled to −70 °C and EtMgBr (Aldrich, 3.0 M solution in Et_2O, 0.33 mL, 1.0 mmol, 2.0 equiv) was added. After stirring for an additional 10 min, a solution of **2.22**[ix] (70.1 mg, 0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (additional 0.5 mL) was added with syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at −70 °C and subsequently EtOH (0.1 mL) and an aq NH_4Cl-solution (1 M, 0.5 mL) were added. The mixture was warmed to rt and an additional 5 mL of the NH_4Cl-solution and 5 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2 x 5 mL), the combined organic extracts were dried and in view of the volatility carefully concentrated to a yellow oil. Flash column chromatography (5:95 Et_2O:pentane) yielded **2.23** as a colorless[x] oil.
The 0.5 g scale synthesis was performed via the same procedure using CuBr•SMe_2 (14.7 mg, 71 µmol, 2.0 mol%) and (*R,S*)-reversed Josiphos (44.5 mg, 75 µmol, 2.1 mol%) in anhydrous CH_2Cl_2 (10 mL); EtMgBr (Aldrich, 3.0 M solution in Et_2O, 1.8 mL, 5.4 mmol, 1.5 equiv); **2.22** (500 mg, 3.6 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (additional 4 mL).

(*R*)-(−)-*E*-ethyl 5-methylhept-3-enoate (**2.23**) was prepared via general procedure E in 84% isolated yield (70 mg/0.5 mmol scale), 95% ee and 98:2 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= −20.0 (c= 2.0, CH_2Cl_2); ^{1}H NMR δ 5.56-5.34 (m, 2H), 4.12 (qd, *J*= 7.1 Hz , 1.3 Hz, 2H), 3.00 (dd, *J*= 6.4 Hz, 0.8 Hz, 2H), 2.10-1.95 (m, 1H), 1.35-1.17 (m, 5H), 0.96 (dd, *J*= 6.8 Hz, 1.3 Hz, 3H), 0.84 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 172.3 (C), 140.3 (CH), 120.0 (CH), 60.4 (CH_2), 38.3 (CH), 38.2 (CH_2), 29.5 (CH_2), 20.0 (CH_3), 14.2 (CH_3), 11.6 (CH_3); MS (GC/MS) *m/z* 170 (M^+, 4), 82 (C_6H_{10}, 55), 55 (C_3H_3O, 100); HRMS calcd. for $C_{10}H_{18}O_2$ 170.1307, found 170.1315. Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[40,xi] column: Chiraldex-B-PM, 60 °C, retention times (min): 42.8 (minor), 45.5 (major). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 60 °C, retention times (min): 95.2 (1,4-product, major), 100.5 (1,4-product, minor), 104.3 (1,6-product).

(*S*)-(+)-*E*-ethyl 5-methylhept-3-enoate (**2.23**) was prepared via general procedure E in 84% isolated yield (70 mg/0.5 mmol scale), 95% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= +20.2 (c= 1.0, CH_2Cl_2); ee was determined by chiral GC analysis for 2-methylbutanoic acid,[40,xi] column: Chiraldex-B-PM, 60 °C, retention times (min): 41.5 (major), 49.0 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 60 °C, retention times (min): 102.8 (1,4-product, major), 108.4 (1,6-product).

(−)-*E*-ethyl 5-methylnon-3-enoate (**2.27a**) was prepared via general procedure E in 85% isolated yield (70 mg/0.5 mmol scale), 97% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= −12.0 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.55-5.32 (m, 2H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.00 (d, *J*= 5.8 Hz, 2H), 2.17-2.03 (m, 1H), 1.34-1.14 (m, 9H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.86 (t, *J*= 6.9 Hz, 3H); ^{13}C NMR δ 172.2 (C), 140.6 (CH), 119.8 (CH), 60.4 (CH_2), 38.2 (CH_2), 36.6 (CH), 36.5 (CH_2), 29.4 (CH_2), 22.7 (CH_2), 20.4 (CH_3), 14.2 (CH_3), 14.1 (CH_3); MS (GC/MS) *m/z* 198 (M^+, 5), 110 (C_8H_{14}, 100), 69 (C_4H_5O, 70), 55 (C_3H_3O, 76); HRMS calcd. for $C_{12}H_{22}O_2$ 198.1620, found 198.1613. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 80 °C,

ix Ethyl sorbate (**2.22**) was purchased from Aldrich, before use this substrate was purified by column chromatography (10:90 Et_2O:pentane) to remove antioxidant and polymer.
x Occasionally the product was polluted by traces of a yellow coloured side product undetectable by GC/MS or NMR.
xi The 2-methylbutanoic acid was obtained by Ru-catalysed $NaIO_4$-oxidation as described in: P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936-3938.

retention times (min): 80.9 (1,4-product, major), 85.8 (1,4-product, minor), 95.1 (1,6-product, minor), 96.0 (1,6-product, major).

(–)-*E*-ethyl 5-methylnona-3,8-dienoate (**2.27b**) was prepared via general procedure E in 57% isolated yield (70 mg/0.5 mmol scale), 92% ee and 97:3 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= –17.6 (c= 1.0, CH_2Cl_2, for 88% ee); ^{1}H NMR δ 5.76 (ddt, *J*= 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H), 5.55-5.31 (m, 2H), 5.02-4.86 (m, 2H), 4.11 (q, *J*= 7.1 Hz, 2H), 2.99 (d, *J*= 6.5 Hz, 2H), 2.20-2.07 (m, 1H), 2.06-1.91 (m, 2H), 1.34 (q, *J*= 7.5 Hz, 2H), 1.23 (td, *J*= 7.13 Hz, 0.5 Hz, 3H), 0.96 (d, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 172.1 (C), 140.0 (CH), 138.8 (CH), 120.3 (CH), 114.2 (CH_2), 60.4 (CH_2), 38.1 (CH_2), 36.1 (CH), 35.9 (CH_2), 31.4 (CH_2), 20.3 (CH_3), 14.1 (CH_3); MS *m/z* 196 (M^+, 1), 108 (C_8H_{12}, 56), 81 (C_5H_5O, 100), 67 (C_5H_7, 59), 55 (C_3H_3O, 57); HRMS calcd. for $C_{12}H_{20}O_2$ 196.1463, found 196.1464. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 80 °C, retention times (min): 83.8 (1,4-product, major), 88.3 (1,4-product, minor), 97.0 (1,6-product, minor), 98.5 (1,6-product, major).

(–)-*E*-ethyl 5,6-dimethylhept-3-enoate (**2.27c**) was prepared via general procedure E in 54% isolated yield (70 mg/0.5 mmol scale), 72% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= –17.6 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.57-5.36 (m, 2H), 4.13 (q, *J*= 7.2 Hz, 2H), 3.01 (d, *J*= 5.5 Hz, 2H), 2.04-1.87 (m, 1H), 1.56-1.44 (m, 1H), 1.25 (td, *J*= 7.1 Hz, 0.7 Hz, 3H) 0.94 (d, *J*= 6.8 Hz, 3H), 0.87-0.78 (m, 6H); ^{13}C NMR δ 172.3 (C), 138.9 (CH), 120.7 (CH), 60.4 (CH_2), 42.9 (CH_2), 38.2 (CH), 32.8 (CH_2), 19.8 (CH_3), 19.6 (CH_3), 17.2 (CH_3), 14.2 (CH_3); MS (GC/MS) *m/z* 184 (M^+, 10), 96 (C_6H_8O, 91), 68 (C_4H_4O, 88), 55 (C_3H_3O, 100); HRMS calcd. for $C_{11}H_{20}O_2$ 184.1463, found 184.1461. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 70 °C, retention times (min): 92.9 (1,4-product, major), 99.0 (1,6-product, minor), 100.0 (1,6-product, major).

(–)-*E*-ethyl 5-ethylnon-3-enoate (**2.30a**)[41] was prepared from **2.29a** using *n*BuMgBr via general procedure E in 88% isolated yield (77 mg/0.5 mmol scale), 96% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= –0.2 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.55-5.37 (m, 1H), 5.30-5.21 (m, 1H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.01 (dd, *J*= 6.9 Hz, 1.3 Hz, 2H), 1.91-1.77 (m, 1H), 1.44-1.15 (m, 11H), 0.92-0.76 (m, 6H); ^{13}C NMR δ 172.2 (C), 139.0 (CH), 121.4 (CH), 60.4 (CH_2), 44.4 (CH), 38.2 (CH_2), 34.5 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3), 14.1 (CH_3), 11.6 (CH_3); MS *m/z* 212 (M^+, 28), 124 (C_9H_{16}, 100), 67 (C_5H_7, 54), 55 (C_3H_3O, 57); HRMS calcd. for $C_{13}H_{24}O_2$ 212.1776, found 212.1786. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 80 °C, retention times (min): 42.7 (1,4-product, major), 43.3 (1,4-product, minor), 46.4 (1,6-product, minor), 47.0 (1,6-product, major).

(+)-*E*-ethyl 5-ethylnon-3-enoate (**2.30a**)[41] was prepared from **2.29a** using EtMgBr via general procedure E in 80% isolated yield (91 mg/0.5 mmol scale), 93% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= +0.2 (c= 1.0, CH_2Cl_2); data was in accordance to (–)-**2.30a**. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 80 °C, retention times (min): 43.0 (1,4-product, major), 46.0 (1,6-product, major), 47.0 (1,6-product, minor).

(–)-*E*-ethyl 5-ethyl-6-methylhept-3-enoate (β,γ-**2.30c**) and (–)-*E*-ethyl 5-ethyl-6-methylhept-2-enoate (α,β-**2.31c**) were prepared via general procedure E in 82% combined isolated yield (84 mg/0.5 mmol scale), 79% ee and 96:4 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= –1.0 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.51-5.36 (m, 1H), 5.33-5.25 (m, 0.7H), 5.12 (ddd, *J*= 15.4 Hz, 8.2 Hz, 1.2 Hz, 0.3H), 4.10 (m, 2H), 3.04 (dd, *J*= 6.9 Hz, 1.3 Hz, 0.9H, β,γ-**2.30c**), 2.40-2.16 (m, *J*= 1.1 Hz, α,β-**2.31c**), 1.72-1.52 (m, 2H), 1.51-1.35 (m, 1H), 1.33-1.14 (m, 5H), 0.98-0.92 (dd, *J*= 6.7 Hz, 2.9 Hz, 2H), 0.89-0.75 (m, 8H); ^{13}C NMR δ 172.9 (C, β,γ-), 172.3 (C, α,β-), 138.6 (CH, β,γ-), 136.6 (CH, α,β-), 129.0 (CH, β,γ-), 122.6 (CH, α,β-), 60.4 (CH_2, α,β-), 60.0 (CH_2, β,γ-), 51.1 (CH, α,β-), 41.2 (CH, β,γ-), 40.6 (CH_2, β,γ-), 38.3 (CH_2, α,β-), 31.4 (CH, α,β-), 31.0 (CH, β,γ-), 27.8 (CH_2, β,γ-),

24.9 (CH_2, α,β-), 22.7 (CH_3, α,β-), 22.6 (CH_3, α,β-), 20.7 (CH_3, β,γ-), 18.9 (CH_3, β,γ-), 14.3 (CH_3, α,β-), 14.2 (CH_3, β,γ-), 12.1 (CH_3, β,γ-), 11.5 (CH_3, α,β-); MS (GC/MS) *m/z* α,β-unsaturated product 198 (M^+, 3), 110 ($C_7H_{10}O$, 100), 95 (C_6H_7O, 62), 69 (C_5H_7, 48), β,γ-unsaturated product 198 (M^+, 5), 110 ($C_7H_{10}O$, 56), 81 (C_5H_5O, 100); HRMS calcd. for $C_{12}H_{22}O_2$ 198.1620, found 198.1627. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 75 °C, retention times (min): 54.6 (α,β-unsaturated-1,6-product, minor), 55.3 (α,β-unsaturated-1,6-product, major), 104.2 (1,4-product, minor), 107.2 (β,γ-unsaturated 1,6-product, minor), 108.5 (β,γ-unsaturated-1,6-product, major), 114.1 (1,4-product, major).

(+)-*E*-ethyl 5-ethyl-7-methyloct-3-enoate (**2.30d**) was prepared via general procedure E in 77% isolated yield (91 mg/0.5 mmol scale), 97% ee and 98:2 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= 9.5 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.46 (dtd, *J*= 15.3 Hz, 7.0 Hz, 0.6 Hz, 1H), 5.22 (ddt, *J*= 15.3 Hz, 9.0 Hz, 1.3 Hz, 1H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.01 (dd, *J*= 7.0 Hz, 1.3 Hz, 2H), 2.01-1.86, (m, 1H), 1.62-1.05 (m, 8H), 0.92-0.65 (m, 9H) (spectrum contains traces of α,β-unsaturated 1,6-product δ 2.38-2.16 (m)); ^{13}C NMR δ 172.2 (C), 139.0 (CH), 121.4 (CH), 60.4 (CH_2), 44.3 (CH_2), 42.3 (CH), 38.2 (CH_2), 28.2 (CH_2), 25.3 (CH_3), 23.5 (CH_3), 21.8 (CH_3), 14.1 (CH_3), 11.6 (CH_3); MS (GC/MS) *m/z* 212 (M^+, 1), 97 (C_7H_{13}, 84), 95 (C_6H_7O, 100), 81 (C_5H_50, 64), 55 (C_3H_3O, 69); HRMS calcd. for $C_{13}H_{24}O_2$ 212.1776, found 212.1768. Regioselectivity and ee were determined by chiral GC analysis, column: Chiraldex-B-PM, 75 °C (isothermic), retention times (min): 125.1 (1,4-product, minor), 134.5 (1,4-product, major), 144.4 (1,6-product, minor), 149.4 (1,6-product, major).

(+)-*E*-ethyl 5-ethyl-7-phenylhept-3-enoate (**2.30e**) was prepared via general procedure E in 73% isolated yield (115 mg/0.5 mmol scale), 90% ee and 98:2 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= 4.1 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.38-7.10 (m, 5H), 5.58 (dt, *J*= 15.3 Hz, 7.0 Hz, 1H), 5.36 (dd, *J*= 15.3 Hz, 8.9 Hz, 1H), 4.19 (q, *J*= 7.1 Hz, 2H), 3.10 (dd, *J*= 6.9 Hz, 1.0 Hz, 2H), 2.82-2.43 (m, 2H), 2.03-1.90 (m, 1H), 1.80-1.20 (m, 7H), 0.89 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 172.0 (C), 142.6 (C), 138.3 (CH), 128.3 (CH), 128.1 (CH), 125.4 (CH), 122.3 (CH), 60.4 (CH_2), 43.9 (CH), 38.1 (CH_2), 36.5 (CH_2), 33.4 (CH_2), 27.8 (CH_2), 14.1 (CH_3), 11.5 (CH_3); MS *m/z* 260 (M^+, 28), 104 (C_8H_8, 79), 91 (C_7H_7, 100); HRMS calcd. for $C_{17}H_{24}O_2$ 260.1776, found 260.1768. Ee was determined by chiral HPLC analysis, column: Whelk (99.9% heptane/*i*PrOH), 40 °C, retention times (min): 23.5 (major), 25.0 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 170 °C, retention times (min): 26.4 (1,4-product), 27.6 (1,6-product).

(−)-*E*-ethyl 5-[(*tert*-butyldiphenylsilyloxy)methyl]hept-3-enoate (**2.30f**) was prepared via general procedure E in 82% isolated yield (197 mg/0.5 mmol scale), 73% ee and 96:4 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= −8.5 (c= 0.8, CH_2Cl_2); ^{1}H NMR δ 7.68- 7.61 (m, 4H), 7.46-7.34 (m, 6H), 5.61-5.50 (m, 1H), 5.42-5.31 (m, 1H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.56 (d, *J*= 6.1 Hz, 2H), 3.02 (dd, *J*= 6.9 Hz, 1.3 Hz, 2H), 2.18-2.08 (m, 1H), 1.33-1.18 (m, 5H), 1.04 (s, 9H), 0.83 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR δ 172.0 (C), 135.8 (CH), 135.6 (CH), 133.9 (C), 129.4 (CH), 127.5 (CH), 123.0 (CH), 67.0 (CH_2), 60.5 (CH_2), 47.0 (CH), 38.4 (CH_2), 26.8 (CH_3), 23.8 (CH_2), 19.3 (C), 14.2 (CH_3), 11.5 (CH_3); MS *m/z* 423 (M^+-H, 0.3), 368 (57), 367 (M- *t*Bu, 100), 227 (TBDPSOEt-*t*Bu, 58), 199 (TBDPSOH-*t*Bu, 50); HRMS calcd. for $C_{22}H_{27}O_3Si$ 367.1729 (M^+-*t*Bu), found 367.1729. Regioselectivity and ee were determined by chiral HPLC analysis for *E*-5-((*tert* butyldiphenylsilyloxy)methyl)hept-3-en-1-ol,[xii] column: chiralcel OD-H (99%

[xii] The alcohol was obtained by DIBAL-H reduction: In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere the ester substrate (1.0 equiv) was dissolved in anhydrous CH_2Cl_2. After 5 min stirring at rt the mixture was cooled to −75 °C and DIBAL-H (1.0M solution in CH_2Cl_2, 2.5 equiv) was added. The solution turned pink/orange. The reaction mixture was stirred for 5 h at −75 °C. Subsequently the reaction mixture was poured into a roundbottom flask with a saturated aq Rochelle's salt-solution, stirred for 1 h at rt and the layers were separated. After extraction with CH_2Cl_2, the combined organic extracts were washed with the aq Rochelle's salt solution (2x), dried and carefully concentrated. The alcohol was used without further purification for chiral HPLC analysis. Reaction was performed for both racemic and enantioenriched ester substrate.

heptane/*i*PrOH), 40 °C, retention times (min): 19.6 (1,4-product), 20.7 (1,6-product, minor), 21.9 (1,6-product, major).

(−)-*E*-ethyl 5-(benzyloxymethyl)hept-3-enoate (**2.30g**) was prepared via general procedure E in 69% isolated yield (123 mg/0.5 mmol scale), 90% ee and >95:5 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= −12.3 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.39-7.23 (m, 5H), 5.61 (dtd, *J*= 7.7 Hz, 6.9 Hz, 0.8 Hz, 1H), 5.40 (ddt, *J*= 15.5 Hz, 8.4 Hz, 1.3 Hz, 1H), 4.50 (s, 2H), 4.13 (q, *J*= 7.1 Hz, 2H), 3.39 (d, *J*= 6.4 Hz, 2H), 3.05 (dd, *J*= 6.9 Hz, 1.3 Hz, 2H), 2.34-2.21 (m, 1H), 1.64-1.49 (m, 1H), 1.34-1.17 (m, 4H), 0.87 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 172.0 (C), 138.5 (C), 135.6 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 123.0 (CH), 73.6 (CH_2), 72.9 (CH_2), 60.5 (CH_2), 44.5 (CH), 38.2 (CH_2), 24.2 (CH_2), 14.2 (CH_3), 11.4 (CH_3); MS *m/z* 276 (M^+, 2), 188 ($C_{13}H_{16}O$, 47), 155 ($C_9H_{15}O_2$, 36), 91 (C_7H_7, 100); HRMS calcd. for $C_{17}H_{24}O_3$ 276.1725, found 276.1728. Ee was determined by chiral HPLC analysis for (*E*)-5-(benzyloxymethyl)hept-3-en-1-ol,[xii] column: chiralcel OD-H (99% heptane/*i*PrOH), 40 °C, retention times (min): 45.1 (1,6-product, minor), 48.9 (1,6-product, major). Regioselectivity was determined by NMR.

(*S*)-(+)-*E*-S-ethyl 5-methylhept-3-enethioate (**2.34**) was prepared via general procedure E in 85% isolated yield (85 mg/0.5 mmol scale), 93% ee and 99:1 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= 11.9 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.52-5.39 (m, 2H), 3.23-3.15 (m, 2H), 2.85 (q, *J*= 7.4 Hz, 2H), 2.13-1.97 (m, 1H), 1.37-1.14 (m, 5H), 0.97 (d, *J*= 6.8 Hz, 3H), 0.85 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 198.5 (C), 142.0 (CH), 119.6 (CH), 47.6 (CH_2), 38.4 (CH), 29.5 (CH_2), 23.3 (CH_2), 19.8 (CH_3), 14.7 (CH_3), 11.7 (CH_3); MS (GC/MS) *m/z* 186 (M^+, 0.2), 97 (C_7H_{13}, 37), 55 (C_3H_3O, 100); HRMS calcd. for $C_{10}H_{18}OS$ 186.1078, found 186.1084. Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[40,xi] column: Chiraldex-B-PM, 60 °C, retention times (min): 41.5 (major), 47.8 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 100 °C, retention times (min): 30.1 (1,4-product, minor), 30.6 (1,4-product, major), 32.5 (1,6-product).

E-S-ethyl 5-methylnon-3-enethioate (**2.36**, EWG=COSEt, R=Me) was prepared via general procedure E in 83% isolated yield (99 mg/0.5 mmol scale), 89% ee and >95:5 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= +9.0 (c= 1.0, CH_3Cl); ^{1}H NMR δ 5.50-5.39 (m, 2H), 3.19 (d, *J*= 5.7 Hz, 2H), 2.84 (q, *J*= 7.4 Hz, 2H), 2.18-2.04 (m, 1H), 1.31-1.16 (m, 9H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.86 (t, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.7 (C), 142.6 (CH), 119.6 (CH), 47.9 (CH_2), 36.9 (CH), 36.7 (CH_2), 29.7 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 20.6 (CH_3), 14.9 (CH_3), 14.3 (CH_3); MS *m/z* 214 (M^+, 10), 124 (M-SEt-Et, 34), 83 (C_6H_{11}, 46), 69 (C_5H_9, 100); HRMS calcd. for $C_{12}H_{22}OS$ 214.1391, found 214.1401.

(*R*)-(−)-*E*-ethyl 5,9-dimethyldeca-3,8-dienoate (**2.38**) was prepared via general procedure E in 34% isolated yield (0.5 g, 3.6 mmol scale, 2% catalyst, 1.2 equiv Grignard reagent), 86% ee and 97:3 regioselectivity (1,6:1,4).
Colorless oil; $[\alpha]_D^{20}$= −14.1 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.55-5.32 (m, 2H), 5.12-5.01 (m, 1H), 4.11 (q, *J*= 7.1 Hz, 2H), 3.00 (d, *J*= 6.2 Hz, 2H), 2.19-2.04 (m, 1H), 2.01-1.86 (m, 2H), 1.61 (d, *J*= 6.2 Hz, 6H), 1.36-1.16 (m, 5H), 0.96 (t, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 172.1 (C), 140.3 (CH), 131.2 (C), 124.5 (CH), 120.1 (CH), 60.4 (CH_2), 38.2 (CH_2), 36.9 (CH_2), 36.2 (CH), 25.7 (CH_2), 25.6 (CH_3), 20.4 (CH_3), 17.6 (CH_3), 14.1 (CH_3); MS *m/z* 224 (M^+, 15), 181 ($C_{11}H_{17}O_2$, 51), 82 (C_6H_{10}, 100), 69 (C_4H_5O, 56); HRMS calcd. for $C_{14}H_{24}O_2$ 224.1776, found 224.1767. Regioselectivity and ee was determined by chiral GC analysis, column: Chiralsil-Dex-CB, 105 °C, retention times (min): 81.3 (1,4-product, major), 94.2 (1,6-product, minor), 94.7 (1,6-product, major).

Synthesis of (*R*)-(−)-*E*-5,9-dimethyldeca-3,8-dien-1-ol (2.39):[42]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, **2.38** (150 mg, 0.67 mmol, 1.0 equiv) was dissolved in anhydrous Et_2O (6.5 mL). The mixture was cooled to 0 °C and $LiAlH_4$ (56 mg, 1.48 mmol, 2.2 equiv) was added in small portions. After stirring for 1 h at 0 °C the reaction was quenched with a 5% aq HCl solution to a pH of 5. Et_2O (5 mL) and H_2O (5 mL) were added

and the layers were separated. After extraction with Et_2O (2x 5 mL), the combined organic extracts were washed with H_2O and brine (10 mL), dried and in view of the volatility carefully concentrated to a colorless oil. Flash column chromatography (10:90 Et_2O:pentane) yielded **2.39** as a colorless oil in 93% yield.

Experimental data:
$[\alpha]_D^{20}$= −21.1 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.46-5.27 (m, 2H), 5.12-5.03 (m, 1H), 3.61 (t, *J*= 6.3 Hz, 2H), 2.25 (q, *J*= 6.4 Hz, 2H), 2.17-2.03 (m, 1H), 1.98-1.88 (m, 2H), 1.70-1.54 (m, 6H), 1.28 (q, *J*= 7.0 Hz, 3H), 0.96 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 140.1 (C), 131.2 (CH), 124.6 (CH), 124.0 (CH), 62.0 (CH_2), 37.0 (CH_2), 36.4 (CH), 36.0 (CH_2), 25.8 (CH_2), 25.7 (CH_3), 20.7 (CH_3), 17.6 (CH_3); MS *m/z* 182 (M^+, 9), 82 (C_6H_{10}, 100), 69 (C_5H_9, 91), 55 (C_4H_7, 80); HRMS calcd. for $C_{12}H_{22}O$ 182.1671, found 182.1678.

Synthesis of (*R*)-(−)-trimethylammonium *E*-5,9-dimethyldeca-3,8-dienyl sulphate (**2.40**):[31]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, **2.39** (60 mg, 0.33 mmol, 1.0 equiv) was dissolved in anhydrous Et_2O (0.5 mL). The mixture was cooled to −5 °C and $ClSO_3H$ (22 µL, 0.33 mmol, 1.0 equiv) was added dropwise. After stirring for 2 h at −5 °C the reaction was quenched with Me_3N at −5 °C (45% aq solution, 0.2 mL). Then H_2O (2 mL) and Et_2O (2 mL) were added and the solution was stirred for 2 min and decanted. This procedure was repeated once with 2 mL Et_2O. The aqueous layer was concentrated to a slightly yellow oil. Flash column chromatography (10:90 MeOH:$CHCl_3$) yielded **2.40** as a colorless oil in 55% yield.

Experimental data:
$[\alpha]_D^{20}$= −10.5 (c= 0.7, $CHCl_3$); lit.[11]= −17.0 (c= 1.89, $CHCl_3$);

^{1}H NMR position:	natural:	synthetic:	^{13}C NMR position:	natural:	synthetic:
1	4.02 (t, *J*= 7.3 Hz)	4.04 (t, *J*= 7.3 Hz, 2H)	1	67.8 CH_2	68.4 CH_2
2	2.37 (m)	2.35 (dd, *J*= 13.0, 7.1 Hz, 2H)	2	32.6 CH_2	32.5 CH_2
3	5.36 (dt, *J*= 15.4, 6.1 Hz)	5.44-5.25 (m, 2H)	3	123.1 CH	123.1 CH
4	5.38 (dd, *J*= 15.4, 7.0 Hz)		4	139.1 CH	139.2 CH
5	2.06 (m)	2.04 (dt, *J*= 13.5, 6.7 Hz, 1H)	5	36.2 CH	36.2 CH
6	1.27 (m)	1.31-1.17 (m, 2H)	6	36.9 CH_2	37.0 CH_2
7	1.92 (m)	1.90 (dd, *J*= 15.2, 7.5 Hz, 2H)	7	25.6 CH_2	25.7 CH_2
8	5.07 (t, *J*= 6.5 Hz)	5.05 (m, 1H)	8	124.5 CH	124.6 CH
10	1.58 (s)	1.56 (s, 3H)	9	131.1 C	131.1 C
11	0.94 (d, *J*= 6.6 Hz)	0.92 (d, *J*= 6.7 Hz, 3H)	10	17.6 CH_3	17.7 CH_3
12	1.67 (s)	1.65 (d, J= 0.9 Hz, 3H)	11	20.5 CH_3	20.4 CH_3
NH	9.75 (br s)	9.39 (br s, 1H)	12	25.5 CH_3	25.7 CH_3
N-CH_3	2.96 (d, *J*= 3.7 Hz)	2.93 (d, *J*= 5.1 Hz, 5H)	N-CH_3	45.3 CH_3	45.7 CH_3
	Impurity:	3.94 (br s)			

2.11 References and notes

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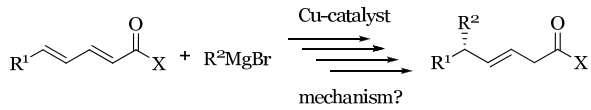
Chapter 3

A Structural Study on the Mechanism of the Enantioselective 1,6-Conjugate Addition

Using the asymmetric 1,6-addition as model reaction, further insight is obtained in the mechanism of copper-catalyzed asymmetric conjugate addition reactions. The 1,6-addition is studied, since the lower reaction rate, compared to the enantioselective 1,4-addition, is probably more suitable for mechanistic investigations. To study the similarity between the mechanisms of the 1,4- and 1,6-addition the effect of structural changes in the substrate on the 1,6-addition are investigated and compared to similar changes in the substrates for 1,4-addition. When the conjugated system is further substituted with methyl group similarities between the 1,4-addition and 1,6-addition are encountered. However, the bulk of the ester and the electron withdrawing group have different effects on the 1,4- and 1,6-addition. Furthermore, the influence of alkene geometry on the 1,6-addition gives interesting results; further studies are needed to understand these findings. Finally, asymmetric 1,8- and 1,10-addition of MeMgBr to multiple unsaturated thioesters proceeds with high regio- and enantioselectivity and modest regio- and enantioselectivity, respectively, while 1,8- and 1,10-addition of EtMgBr to multiple unsaturated esters gives modest regio- and low enantioselectivity. Based on these results a preliminary model for extended conjugate additions is proposed. Furthermore, the C4-olefin is probably involved in the enantiodiscriminating step of the mechanism. Further studies are needed to validate both conclusions.



3.1 An introduction to the mechanism of the ACA with Grignard reagents

Recently, the mechanism of the Cu-catalyzed ACA[1] of Grignard reagents to α,β-unsaturated carbonyl compounds using ferrocenyl ligands has been studied extensively.[2] The studies started with the identification of the precatalysts, formed from CuBr and either JosiPhos (**L3.1**) or reversed JosiPhos (**L3.2**). Interestingly, at rt a solvent dependent dimerization of the precatalyst was observed by ESI-MS, IR spectroscopy, electrochemistry and, for **L3.2**, by X-ray analysis (Scheme 3.1).

Furthermore, by electrochemistry at −78 °C the redox potentials of the Cu-**L3.1** and Cu-**L3.2** precatalyst were determined. Since it was found that the Cu-**L3.2** dimer is easier to oxidize than the Cu-**L3.1** dimer using electrochemistry, it was concluded that Cu-**L3.2** is more electron rich. This difference in electronics might account for the higher reactivity of the Cu-**L3.2** complex in the ACA of Grignard reagents of the less reactive aryl substituted α,β-unsaturated ester substrates (see also paragraph 1.8.3).

The influence of several reaction parameters on the 1,4-ACA was studied as well. First of all, the effect of the nature of the solvent on the reaction was examined (Table 3.1). As is described in paragraph 1.5, the monoalkylmagnesium bromide is in equilibrium with the dialkylmagnesium and magnesium dibromide species in solution via the Schlenk equilibrium (Figure 3.1). From this study it was concluded that in solvents where the monoalkylmagnesium bromide is the dominant species, the 1,4-ACA products are formed with good regio- and enantioselectivity (entry 1 to 4). In contrast, when the dialkylmagnesium species is the preferred one, either by the use of THF as solvent (entry 5), or by the use of Me_2Mg in CH_2Cl_2 (entry 6), or finally by shifting the Schlenk equilibrium by the addition of dioxane (entry 7), loss of both regioselectivity towards the 1,4-product and enantioselectivity was observed. Furthermore, the difference in solvation might partially account for the observed profound effect of the solvent on the reaction as well.

Scheme 3.1. *Solvent dependent dimerization of the precatalysts.*

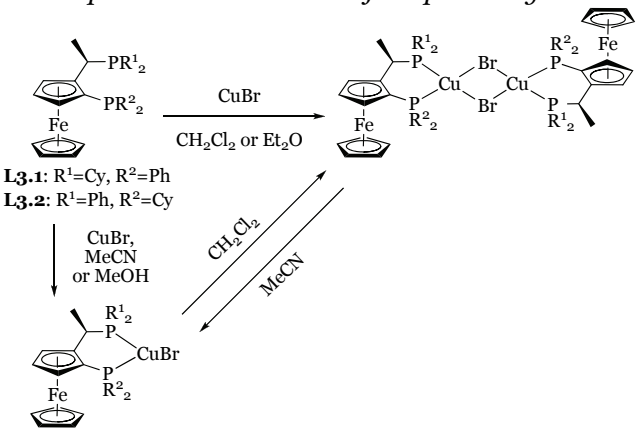
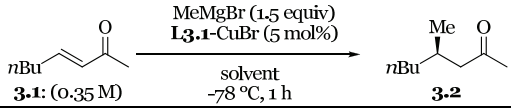


Table 3.1. *Solvent dependency of the 1,4-ACA.*



entry	solvent	remark	conversion	regio (1,4:1,2)	ee
1	CH_2Cl_2		88%	86:14	92%
2	toluene		89%	88:12	91%
3	*t*BuOMe		90%	97:3	96%
4	Et_2O		87%	83:17	87%
5	THF		67%	2:98	2%
6	CH_2Cl_2	using dioxane (1 equiv)	35%	75:25	80%
7	CH_2Cl_2	using Me_2Mg (1.5 equiv)[a]	25%	42:58	75%

[a] Instead of MeMgBr.

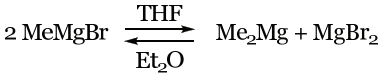
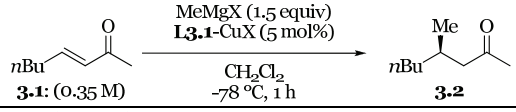


Figure 3.1. *The Schlenk equilibrium for MeMgBr.*

Furthermore, the dependency of the ACA reaction on the halide was investigated (Table 3.2). It was concluded that the presence of bromide, in either the Grignard reagent or the Cu-salt, is essential to achieve high regio- and enantioselectivity (entry 1 to 4 vs. entry 5). Furthermore, the presence of iodide in the Grignard reagent gives lower regio- and enantioselectivity (entry 6 and 7).

Having established the importance of the presence of bromide and, in particular, MeMgBr to obtain good regio- and enantioselectivity in ACA, the complexes formed from the catalyst precomplex Cu-**L3.1** and, respectively, MeMgBr and MeLi were studied (Scheme 3.2, next page). Using MeMgBr, predominantly species **3.3** and traces of unidentified species **3.4** were formed (Scheme 3.2a). Species **3.4** was shown to be formed from **3.3** in solution as the only complex when the solution was exposed to air, instead of an inert atmosphere. The structure of **3.4** remained elusive. In spite of the fact that **3.4** gave high enantioselectivity in reaction with **3.1,** the role of **3.4** in the mechanism was deemed unlikely since the ACA reaction is normally performed under a N_2 atmosphere. However, recent results[i] for the related

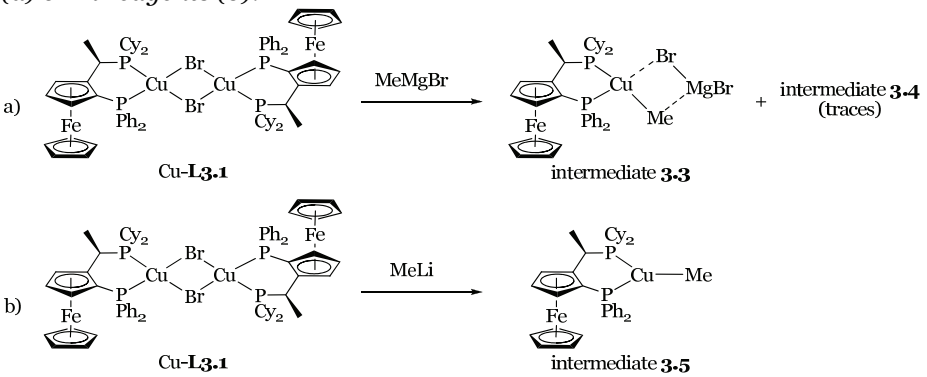
Table 3.2. *Halide dependency of the ACA.*



entry	CuX	Grignard reagent	conversion	regio (1,4:1,2)	ee
1	CuBr	MeMgBr	88%	86:14	92%
2	CuCl	MeMgBr	95%	85:15	94%
3	CuI	MeMgBr	85%	85:15	90%
4	CuBr	MeMgCl	88%	82:18	91%
5	CuCl	MeMgCl	99%	50:50	72%
6	CuBr	MeMgI	94%	77:23	30%
7	CuI	MeMgI	95%	71:29	36%

[i] Unpublished results.

Scheme 3.2. *Cu complexes formed from transmetallation of Cu-**L3.1** with Grignard (a) or Li reagents (b).*



AAA have shown that an inert atmosphere is not required for the AAA to proceed with high regio- and enantioselectivity and thus the role of species **3.4** in the mechanism might have to be reinvestigated.

Mixing precatalyst Cu-**L3.1** with MeLi gave species **3.5** (Scheme 3.2b). Interestingly, also by addition of dioxane to a mixture of MeMgBr and Cu-**L3.1**, again driving the Schlenk equilibrium to favor Me_2Mg, species **3.5** was formed. Since **3.5** gave poor results for the ACA it was concluded that species **3.3** is the active species in the mechanism for ACA.

Unfortunately, the reaction of intermediate **3.3** with α,β-unsaturated esters was too fast to observe any further intermediates of the 1,4-ACA mechanism by NMR spectroscopy. Further information on the mechanism of ACA was acquired by kinetic studies. For these studies the reaction progress for the ACA of EtMgBr to methyl crotonate was studied for several initial concentrations of Grignard reagent, substrate and catalyst.[ii] Increased initial concentrations of either Grignard reagent or substrate gave an increase in rate, suggesting that both reagents are involved in the rate determining step. Furthermore, a 1.17th reaction order with respect to the catalyst indicates that the active catalyst is a mononuclear complex.[iii]

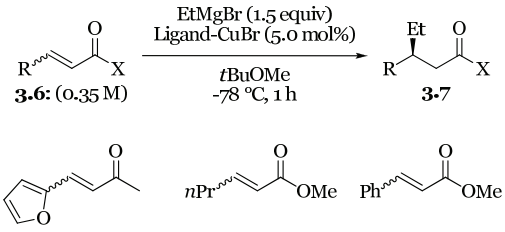
Another important observation for this system relates to the olefin geometry of the substrates (Table 3.3). The ACA of EtMgBr to both *E*- and *Z*-isomers of the enone **3.6a** (entries 1 and 2) led to the same enantiomer of product **3.7a** in 95 % ee. By contrast, for the α,β-unsaturated ester **3.6b** the use of the *E*- or the *Z*-isomer led to opposite enantiomers of product **3.7b** with the same enantioselection (entries 3 and 4). Furthermore, for the less reactive α,β-unsaturated ester **3.6c** reaction of the *E*-isomer gave the product **3.7c** in excellent ee (entry 6), while reaction of *Z*-**3.6c** gave the enantiomer of **3.7c** in lower ee (entry 7).

The effect of olefin geometry on the ee of the products was attributed to a *Z-E* isomerization, which for several substrates competes with the ACA. The isomerization of the substrates was observed by quenching of the reactions before

[ii] The data for these studies was obtained by analyzing aliquots taken at several time intervals by chiral GC. Due to the high reaction rate, even at low temperatures, the kinetics might need further validation by in-situ data using Raman, UV or IR spectroscopy.

[iii] The mononuclearity was confirmed by an ACA reaction of the mixed precomplex of **L3.1**-Cu-$(Br)_2$-Cu-**L3.2** to methyl cinnamate, see ref 2.

Table 3.3. *Influence of the olefin geometry on ACA.*

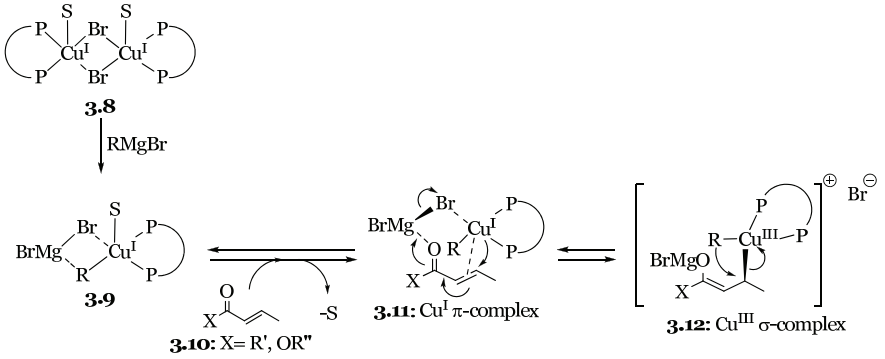


entry	substrate	catalyst	conversion(%)	*Z*:*E* substrate (%)	ee(%)
1	*E*-**3.6a**	**L3.1**	100	-	95 (+)
2	*Z*-**3.6a**	**L3.1**	100	-	95 (+)
3	*E*-**3.6b**	**L3.1**	100	-	90 (*R*)
4	*Z*-**3.6b**	**L3.1**	100	-	90 (*S*)
5	*Z*-**3.6b**	**L3.1**	50[a]	99:1	90 (*S*)
6	*E*-**3.6c**	**L3.2**	100	-	98 (*S*)
7	*Z*-**3.6c**	**L3.2**	100	-	53 (*R*)
8	*Z*-**3.6c**	**L3.2**	10[b]	94:6	59 (*R*)

[a] Reaction was stopped after 50% conversion. [b] Reaction was stopped after 10% conversion.

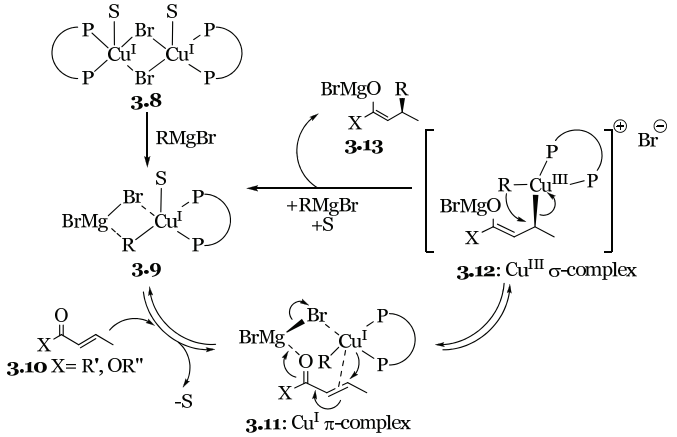
full conversion was reached. While for **3.6b** exclusively *E*-**3.6b** was recovered (entry 5), under the reaction conditions *Z*-**3.6c** had partly isomerized to *E*-**3.6c**. Interestingly, control experiments have shown that both the chiral Cu complex and the Grignard reagent need to be present for isomerization to occur. Analogous to earlier studies[3,4] the *E-Z* isomerization was proposed to involve a Cu^{III} σ-intermediate (Scheme 3.3). Although Cu^{III} species have been elusive for over decades, cyano group-stabilized Cu^{III} species, formed from cyclohexenones and alkyl lithium reagents, were recently observed using low temperature NMR spectroscopy.[5]

Scheme 3.3. *Mechanism for E-Z isomerization of ACA substrates.*



Used abbreviations: S=solvent (in this case *t*BuOMe). P-P=JosiPhos or reversed JosiPhos ligand. Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^{I}-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules. 3) *Trans* or *cis* relationship with respect to the distinct phosphor atoms of the ligand are not taken into account in the depiction of this mechanism.

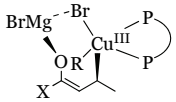
Scheme 3.4. *Hypothetical model for 1,4-ACA with Grignard reagents.*



Used abbreviations: S=solvent (in this case *t*BuOMe). P-P=JosiPhos or reversed JosiPhos ligand. Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^{I}-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules. 3) *Trans* or *cis* relationship with respect to the distinct phosphor atoms of the ligand are not taken into account in the depiction of this mechanism.

Combining all data on the ACA with Grignard reagents a mechanism was proposed (Scheme 3.4). In the mechanism the dimeric precatalyst (**3.8**, Cu-**L3.1** or Cu-**L3.2**) and a Grignard reagent form the active catalyst **3.9**. Interaction of **3.9** with substrate **3.10** then, reversibly, forms the Cu^{I} π-complex **3.11**.[6] Subsequently, oxidative insertion and formation of the enolate from **3.11** gives, again reversibly, the d8 Cu^{III} σ-complex **3.12**. Finally, reductive elimination forms the ACA-product **3.13** and reforms the active catalyst complex **3.9** by interaction with another Grignard reagent.

In the original paper[2] the Cu^{III} species **3.12** was depicted as 18 electron 5-coordinated Cu^{III}-species (**3.14**, Figure 3.2), which presumably has a square pyramidal geometry with the bromide directly coordinated to the copper. In the proposed complex **3,14**, the bromide chelates to the magnesium enolate. By low level calculations[7] (PM3-level) **3.14** is proposed to have a chairlike seven-membered ring conformation. The structure for **3.14** is debatable since all known stable
Cu^{III}-species[5] have been assigned to be 16 electron structures with a square planar geometry by interpretation[5c] of ^{1}H and $^{1}H,^{13}C$-HMBC NMR spectra. As the depicted 16 electron Cu^{III}-species in Scheme 3.4, **3.12** is charged and adopts a distorted square planar geometry to facilitate interaction with the JosiPhos (**L3.1**) or reversed JosiPhos (**L3.2**) ligands. Presumably, this complex has a bromide as counterion.



3.14: Cu^{III} σ-complex

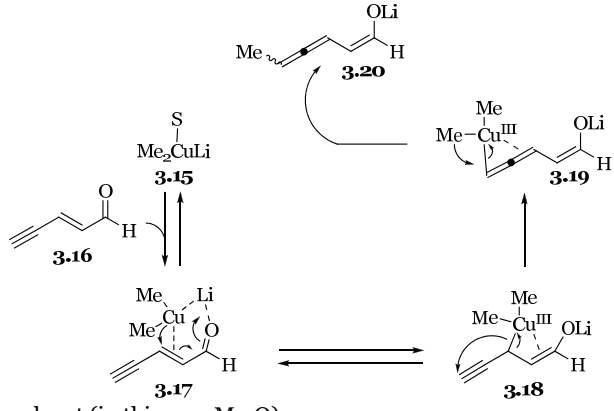
Figure 3.2. *Originally proposed structure of the Cu^{III} σ-complex.*

In the paper of Harutyunyan et al.[2] a preliminary model for the enantioselection in the 1,4-ACA with Grignard reagents was proposed. By low-level calculations (PM3-level) the enantioselectivity was proposed to be determined in the seven-membered intermediate of the debatable 18 electron 5-coordinated Cu^{III}-species **3.14**. Further research, in particular high-level calculations, is definitely necessary to validate this model for enantiodiscrimination.

3.2 An introduction to the mechanism of 1,6-conjugate addition

Investigation of the mechanism of the stoichiometric 1,6-addition of Gilman reagents to enynes has been pioneered by Krause and co-workers[8] and has provided insight in the mechanism of this reaction. A proposed mechanism[9] for the 1,6-addition to 2-en-4-ynoates (**3.16**) is depicted in Scheme 3.5. The initial step in the mechanism is the formation of π-complex **3.17**. Similar complexes as **3.17** have been observed and identified by NMR spectroscopy[10,11] and their role in the mechanism has been confirmed by kinetic studies.[12] As next step in the mechanism, formation of Cu^{III} σ-complex **3.18** via oxidative addition has been proposed. Subsequent copper migration, forming Cu^{III} σ-complex **3.19**, and reductive elimination, giving product **3.20** and reforming a Cu^{I} species, have been proposed on the basis of high level calculations to be the energetically favored pathway from intermediate **3.18**.[9] For this mechanism kinetic isotope effect studies have identified the Cu-migration as the rate determining step.[13] Furthermore, the high regioselectivity of the reaction was rationalized by the disruption of the conjugated system by C-C bond formation at the β-position, giving a high energy barrier for 1,4-addition.

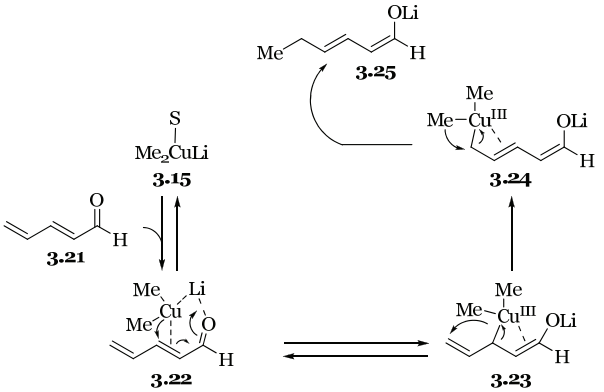
Scheme 3.5. *Proposed mechanism for cuprate 1,6-addition to a 2-en-4-ynal.*[9]



Used abbreviation: S=solvent (in this case Me_2O).
Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^{I}-species. 2) The solvation of Li is not depicted.

The 1,6-addition of a Gilman reagent to dienoates[iv] has been calculated by Nakamura and co-workers to proceed in a similar fashion (Scheme 3.6). The activation barriers between the pathways for 1,4-addition and 1,6-addition pathways are closer in energy for these molecules than for the enynes, indicating that the regioselectivity is usually lower for these systems.

Scheme 3.6. *Proposed mechanism for cuprate 1,6-addition to a dienal.*[9]



Used abbreviation: S=solvent (in this case Me_2O).
Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^{I}-species. 2) The solvation of the Li is not depicted.

3.3 Investigating the ACA mechanism

To further develop our understanding of the mechanism of 1,4-ACA further research is required (see also paragraph 7.7). Especially, combined detailed kinetic studies and molecular modelling might shed light on the mechanism of 1,4-ACA. However, the high reaction rate of the 1,4-ACA with Grignard reagents, even at low temperatures, complicates these studies. A model system for the investigation of this mechanism is thus highly warranted. The development of the asymmetric 1,6-addition (see chapter 2), which requires slightly higher reaction temperatures and longer reaction times than the 1,4-ACA (2 h reaction time at −78 °C vs. 16 h reaction time at −70 °C for 1,6-ACA), provides such a model system for the investigation of the mechanism of the ACA with Grignard reagents. Especially since the mechanisms of cuprate 1,4-addition[2] and cuprate 1,6-addition[9] have been proposed to proceed via similar intermediates (see paragraph 3.1 and 3.2).

Unfortunately, preliminary low temperature NMR experiments have shown that at the concentration necessary for NMR spectroscopy, even the 1,6-addition is too fast to observe any intermediates.[v] Still, a comparison of the influence of several factors on the 1,4-ACA and 1,6-ACA might allow a better understanding of the mechanism and the stereochemical pathway of ACA with Grignard reagents. In this chapter the influence of several structural features of the substrates on the 1,6-ACA is described. Furthermore, a comparison is made between the effect of these structural features on the 1,4-ACA and the 1,6-ACA.

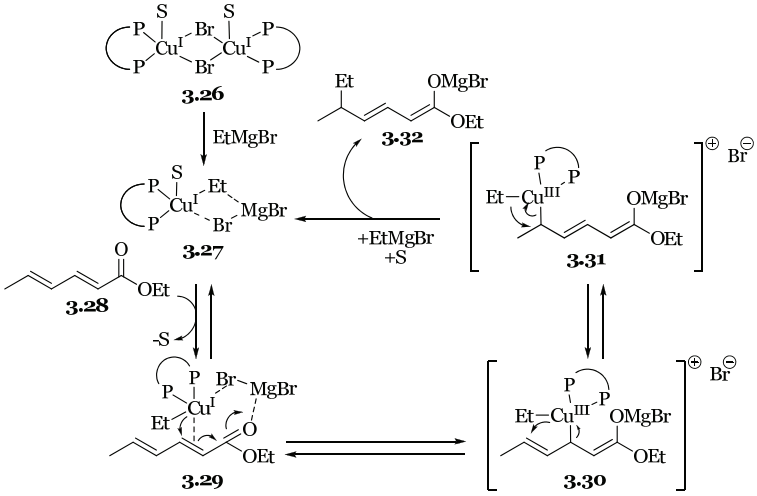
[iv] A dienal was taken as model system.

[v] Unpublished results

3.4 Mechanistic models for 1,6-ACA

Based on the recent mechanistic studies on CA of Grignard reagents[2] and the mechanism proposed by Krause and Nakamura for 1,6-CA[9] the catalytic cycle depicted in Scheme 3.7 can be proposed for asymmetric 1,6-addition. The cycle starts with formation of reactive complex **3.27** from the dimeric resting state **3.26** of the catalyst. Presumably, **3.27** forms a Cu^{I} π-complex **3.29** with substrate **3.28**, followed by formation of d8 Cu^{III} σ-complex **3.30**. Next, **3.30** undergoes sequential copper migration to the remote position, possibly via an 18 electron σ/π-allyl intermediate, to give intermediate **3.31**. The catalytic cycle is completed by reductive elimination to form product **3.32** and reformation of complex **3.27**.

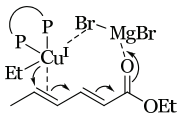
Scheme 3.7. *Proposed mechanism for asymmetric 1,6-addition with Grignard reagents.*



Used abbreviations: S=solvent (in this case CH_2Cl_2). P-P= reversed JosiPhos ligand.
Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^{I}-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules. 3) *Trans* or *cis* relationship with respect to the distinct phosphor atoms of the ligand are not taken into account in the depiction of this mechanism.

However, the mechanism depicted in Scheme 3.7 is not the only possible mechanistic pathway[vi] for the enantioselective 1,6-addition. Instead of the formation of d8 Cu^{III} complex **3.30** the mechanism can proceed via the second Cu^{I} π-complex with the terminal olefin (Figure 3.3, next page, **3.33**) before intermediate **3.31** is formed. The formation of intermediate **3.33** in the mechanism would have to compete with the formation of **3.30**. Complex **3.30** might be responsible for the formation of traces of 1,4-addition side-product with enantioselectivity observed in the 1,6-ACA.

[vi] A direct C-C bond formation from intermediate **3.30** via an allylic-type transfer of the R-group to the 1,6-position seems unlikely in view of the results for the 1,8- and 1,10-addition (vide supra).



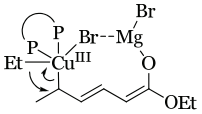
3.33

Figure 3.3. *An alternative for intermediate* ***3.30*** *in the 1,6-ACA mechanism.*

Finally, although it seems unlikely in view of the catalytic activity of the Cu-JosiPhos-type complexes for 1,4-ACA and the formation of traces of 1,4-addition side product, a mechanism where the Cu-**L3.2** complex directly coordinates to the terminal olefin can not be excluded.

An open question in all the proposed mechanisms for 1,6-ACA is the stereochemical course of the reaction and especially at what stage the enantioselectivity is determined. A first hypothesis is that either in the Cu^{I} π-complex with the internal olefin **3.29** or the Cu^{III} complex **3.30** at the β-position the stereochemistry is already fixed and subsequently transferred to the remote position to give the 1,6-addition product with high ee.

Alternatively, the stereochemical discrimination might occur at the δ-position. This might either occur by coordination of the Cu-catalyst to the dienolate via the olefins or via chelation to the magnesium bromide, coordinated at the oxygen of the dienolate, in a nine-membered intermediate (**3.34**, Figure 3.4). The latter is analogous to the debatable, originally proposed,[2] seven-membered intermediate for the 1,4-ACA with Grignard reagents.



3.34

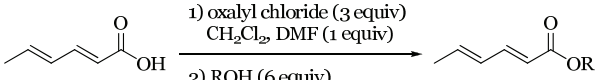
Figure 3.4. *A nine-membered intermediate possibly responsible for stereochemical discrimination in 1,6-ACA.*

3.5 Synthesis of substrates

Methyl, *iso* propyl and *tert* butyl sorbate (**3.36a** to **3.36c**) were prepared from sorbic acid, by in-situ formation of the acid chloride and subsequent reaction with the corresponding alcohol in good yields (Scheme 3.8).[14]

A number of substrates with distinct electron withdrawing groups were prepared via a variety of routes (Scheme 3.9). Wittig reaction of **3.38**[15] with aldehyde **3.37** gave thioester **3.39** in good yield and high selectivity. HWE reaction[16] of **3.37** with deprotonated **3.40** gave ketone **3.41** in good yield. Sulfonylpyridine **3.43** was prepared via an aldol-type reaction of the methyl sulfonyl pyridine anion[17] (prepared from **3.42**) with **3.37** and subsequent dehydration[17] with MsCl and

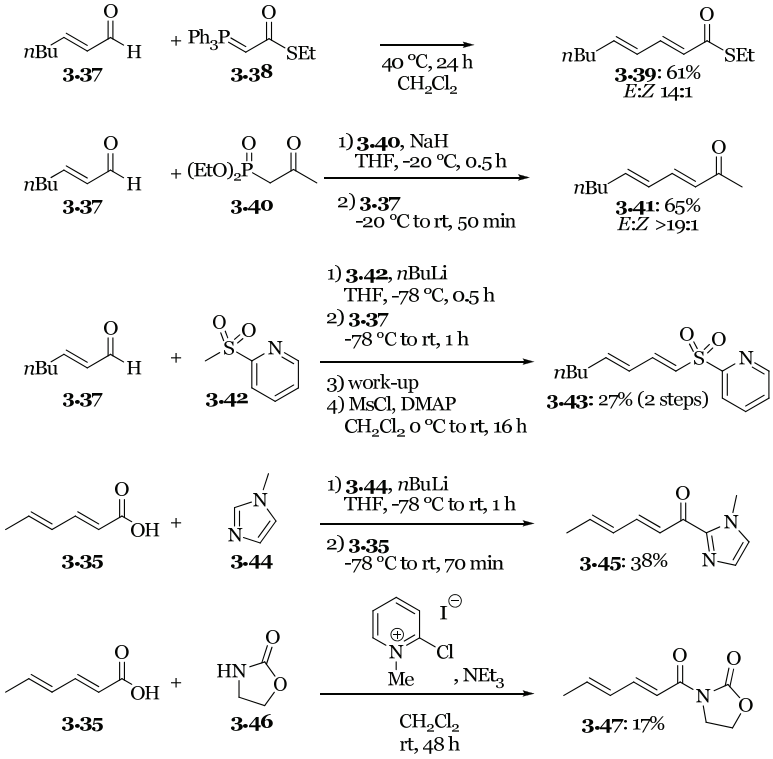
Scheme 3.8. *Synthesis of several alkyl sorbates.*



3.35

3.36a R=Me: 77%
3.36b R=*i*Pr: 83%
3.36c R=*t*Bu: 83%

Scheme 3.9. *Synthesis of several α,β,γ,δ-bisunsaturated Michael acceptors.*

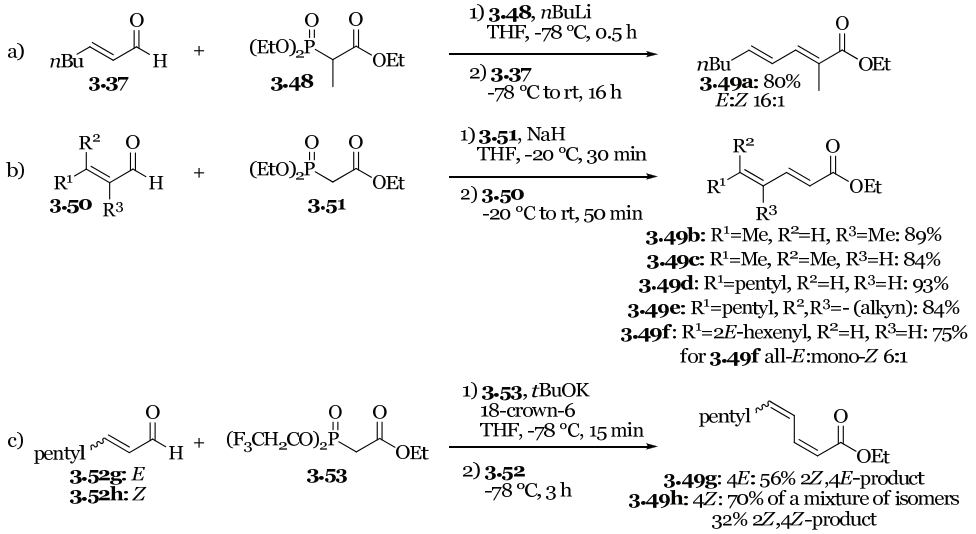


DMAP in low yield. Direct ketone formation[18] of sorbic acid (**3.35**) with deprotonated 2-methylimidazole (**3.44**) gave imidazolinone **3.45** in reasonable yield. Finally, using 2-chloro-1-methylpyridinium as coupling reagent, oxazolidinone **3.47** was prepared[19] from sorbic acid (**3.35**) in low yield.

Several methyl substituted α,β,γ,δ-bisunsaturated esters were prepared using HWE reactions (Scheme 3.10, next page). α-Methyl substituted α,β,γ,δ-bisunsaturated substrate **3.49a** was prepared via HWE reaction with reagent **3.48**[20] in good yield and *E*:*Z* selectivity (Scheme 3.10a). The γ- and δ-methyl substituted substrates were prepared via HWE reaction with reagent **3.51**[16] in excellent yield and exclusively *E*-**3.49b** and *E*-**3.49c** were obtained (Scheme 3.10b). Finally, β-methyl substituted substrate **3.49i** was prepared via a Pd-catalyzed oxidative Heck reaction[21] under an O_2 atmosphere (Scheme 3.11, next page). Unexpectedly, the product **3.49i** proved extremely volatile and was obtained in low yield.

All *E*- and *Z*-isomers of **3.49d** were prepared using HWE reactions. The bisunsaturated ester 2*E*,4*E*-**3.49d** was obtained via HWE reaction of **3.51**[16] with **3.50d** in excellent yield and *E*:*Z*-selectivity (Scheme 3.10b). 2*E*,4*Z*-**3.49j** was obtained after two synthetic steps. First, HWE reaction gave **3.49e**, and this product was subsequently reduced using *Z*-selective hydrogenation with Lindlar catalyst[22] (Scheme 3.12) to give exclusively 2*E*,4*Z*-**3.49j** with some over-reduced product (**3.57**). A *Z*-selective HWE reaction[23] of **3.52g** with HWE-reagent **3.53** gave 2*Z*,4*E*-**3.49g** in reasonable yield (Scheme 3.10c). Finally, a mixture of predominantly 2*Z*,4*Z*-**3.49h** with some of its isomers was obtained via the

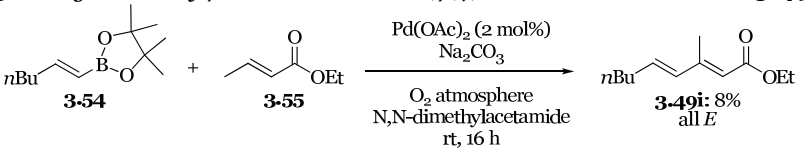
Scheme 3.10. *HWE reactions for the synthesis of several unsaturated esters.*



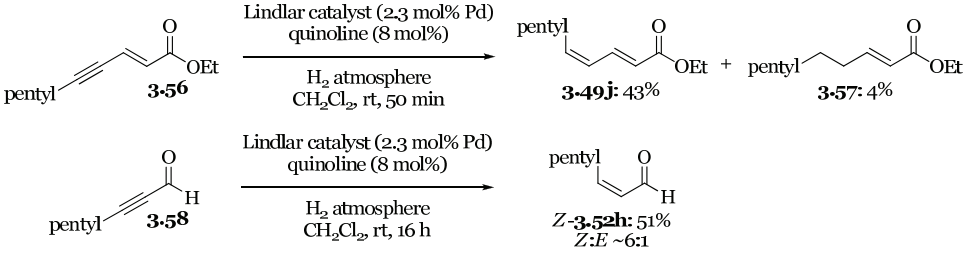
Z-selective HWE reaction[23] from *Z*-**3.52h**. The 4*E*-olefin was partially found in the product, which means that the 4*Z*-olefin isomerized towards the 4*E*-olefin during this reaction. The isomerization takes place either when *Z*-**3.52h** is exposed to the reaction conditions, or in one of the intermediates towards **3.49h**. Fortunately, most of the isomers were separable by column chromatography. The 2*Z*,4*Z*- (**3.49h**) and 2*Z*,4*E*-isomers (**3.49g**), however, were not separable.

Both the ester (**3.49f**, Scheme 3.10b) and thioester (**3.61**, Scheme 3.13) substrate for 1,8-addition were obtained via HWE reaction in good yield and reasonable *E*-selectivity. Compound **3.49f** was further elaborated to give two substrates for 1,10-addition via a reduction, IBX-oxidation, HWE reaction sequence in reasonable yield over 3 steps (**3.49k** and **3.63**, Scheme 3.14).

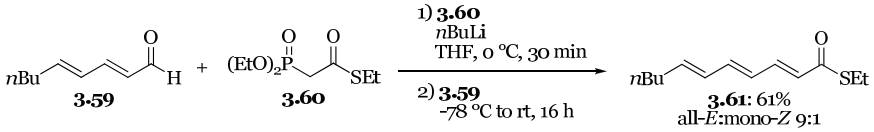
Scheme 3.11. *Synthesis of β-Me substituted α,β,γ,δ-bisunsaturated ester* ***3.49i****.*



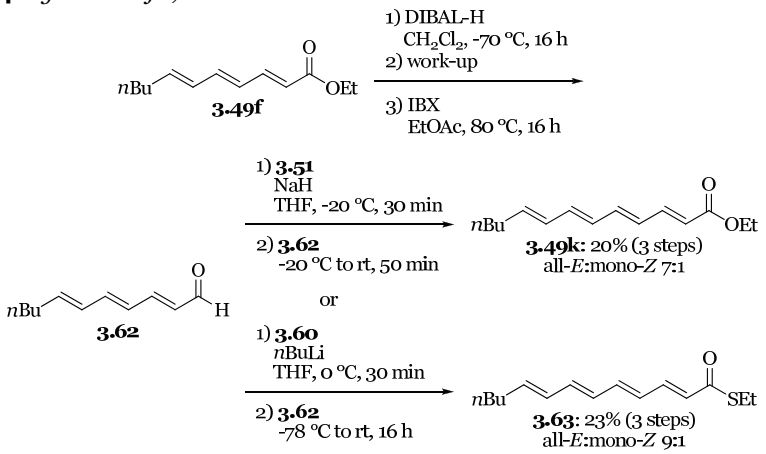
Scheme 3.12. *Reduction of alkynes to Z-olefins using Lindlar catalyst.*



Scheme 3.13. *Synthesis of the thioester 1,8-ACA substrate.*



Scheme 3.14. *Synthesis of 1,10-ACA substrates.*

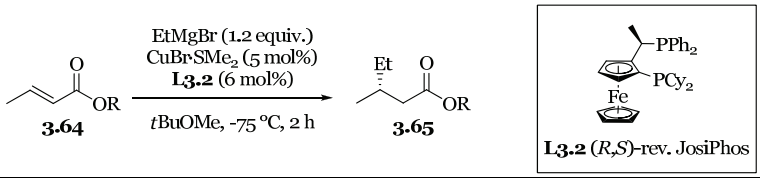


3.6 The influence of the ester size on the 1,6-ACA

In the 1,4-ACA of Grignard reagents to α,β-unsaturated esters,[24] the alkyl substituent on the ester has a profound influence on the enantioselectivity of the reaction (Table 3.4). Using the reversed JosiPhos catalyst (**L3.2**) the best result with respect to enantioselectivity was obtained for the methyl ester (entry 1), while for more bulky esters the enantioselectivity of the 1,4-ACA dropped significantly (entry 2 and 3).

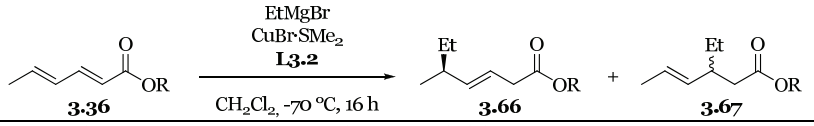
For the asymmetric 1,6-addition of Grignard reagents to sorbates using **L3.2** the reverse trend was observed (Table 3.5, next page). The methyl ester (**3.36a**) gave reasonable enantioselectivity (entry 1), while with the increase of the bulkiness of the ester an increase of the enantioselectivity of the reaction was observed (entry 2

Table 3.4. *The influence of the ester size on the 1,4-ACA.*



entry	substrate	R	product	conversion (%)	ee (%)
1	**3.64a**	Me	**3.65a**	96	92
2	**3.64b**	Et	**3.65b**	96	78
3	**3.64c**	*i*Pr	**3.65c**	98	54

Table 3.5. *The influence of the ester size on the 1,6-ACA.*[a]



entry	substrate	R	product	yield (%)	**3.66**:**3.67**[b]	ee[b,c] (%)
1	**3.36a**	Me	**3.66a**	64	>99:1	75 (*S*)
2	**3.36d**	Et	**3.66d**	84	98:2	95 (*S*)
3	**3.36b**	*i*Pr	**3.66b**	82	99:1	97 (*S*)
4	**3.36c**	*t*Bu	**3.66c**	88	98:2	98 (*S*)

[a] Conditions: a solution of **3.36** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **3.36**). [b] Ratio **3.66**:**3.67** and ee's were determined by chiral GC. [c] Absolute configuration of **3.66** was determined by conversion to a known compound (see experimental section).

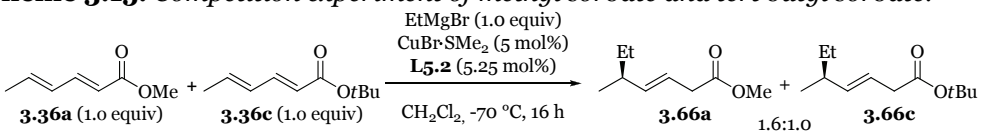
and 3). For *tert* butyl sorbate (**3.36c**) the 1,6-product **3.66c** was obtained with an unprecedented 98% ee (entry 4). Regioselectivity was excellent for all sorbates and seems not to be influenced by ester size.

To study the correlation between enantioselectivity and reaction rate, a competition experiment for the 1,6-ACA of EtMgBr to methyl (**3.36a**) and *tert* butyl sorbate (**3.36c**) was performed (Scheme 3.15). Based on the ratio of the observed products[vii] the 1,6-ACA to methyl sorbate is around 1.6 times faster than the 1,6-ACA to *tert* butyl sorbate.

Since the difference in enantioselectivity and reaction rate might be attributed to either the bulkiness of the alkyl esters or the electronic changes to the conjugated system, the IR spectra of the sorbates were compared (Figure 3.5 and Table 3.6). With increased bulkiness of the ester the C=O stretch frequencies are slightly lower (entry 4 vs. entry 1), while the C=C stretch frequencies are unaffected. The small changes in the frequencies indicate that the strength of the Michael acceptor is only slightly influenced by the bulkiness of the ester. The C=O bond of *tert* butyl sorbate (**3.36c**) is slightly weaker according to the IR spectra and thus the *tert* butyl sorbate is a slightly better Michael acceptor than methyl sorbate. The profound effect of the different esters on the enantioselectivity of the 1,6-ACA can thus mainly be attributed to the sterics of the ester. This conclusion is in agreement with results for the Michael addition of thiols to several α,β-unsaturated esters,[25] for which the slower reaction rate for more bulky esters was attributed to steric effects.[25]

The fact that the positive effect of the *tert* butyl ester group on the 1,6-ACA is not limited to the use of EtMgBr was illustrated by the addition of several Grignard reagents to *tert* butyl sorbate (**3.36c**, Table 3.7). The reaction with either

Scheme 3.15. *Competition experiment of methyl sorbate and tert butyl sorbate.*



[vii] The ratio of the remaining substrates could not be compared since degradation of the sorbates was observed under reaction conditions.

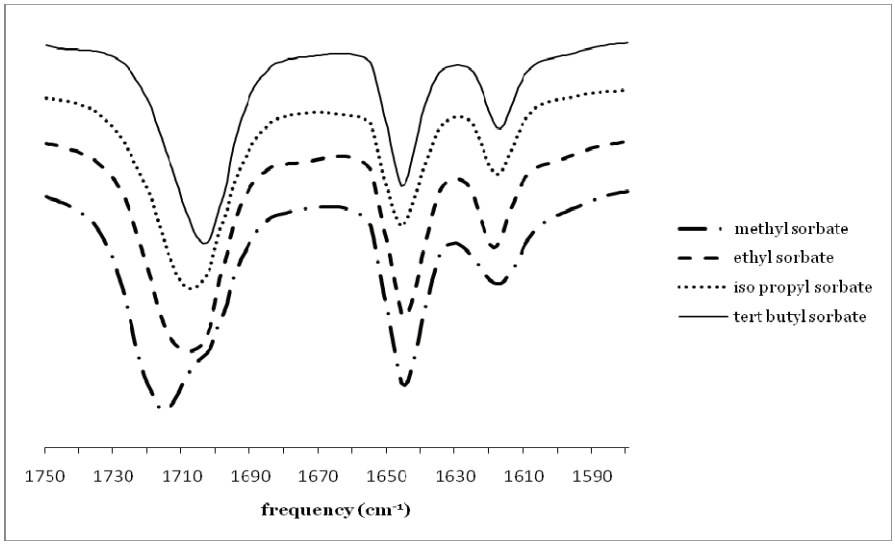


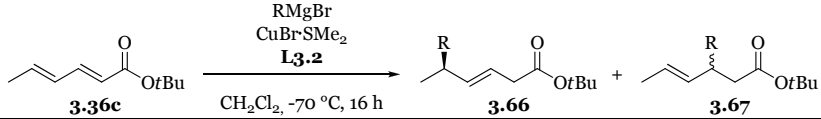
Figure 3.5. *C=O and C=C stretch region of the IR spectra of* ***3.36a*** *to* ***3.36d****.*

Table 3.6. *Frequencies for the C=O and C=C stretch vibrations of the IR spectra for* ***3.36a*** *to* ***3.36d****.*

entry	substrate	R	C=O stretch vibration (cm^{-1})	C=C stretch vibrations (cm^{-1})	
1	**3.36a**	Me	1716	1618	1645
2	**3.36d**	Et	1708	1619	1645
3	**3.36b**	*i*Pr	1708	1618	1645
4	**3.36c**	*t*Bu	1704	1617	1646

hexylmagnesium bromide or the branched *iso* pentylmagnesium bromide gave the 1,6-addition products in excellent ee (entry 1 and 2). Finally, the 1,6-addition of phenethylmagnesium bromide to *tert* butyl sorbate gave product **3.66g** in reasonable conversion, low yield and good regio- and enantioselectivity (entry 3). This is in sharp contrast to the 1,6-addition of phenethylmagnesium bromide to ethyl sorbate (**3.66d**) which gave no observable conversion to the 1,6-addition product (see paragraph 2.5). This result might be explained by the trapping of an intermediate in the 1,6-addition to ethyl sorbate, while for the 1,6-addition to

Table 3.7. *The influence of the ester size on the 1,6-ACA.*[a]



3.36c **3.66** **3.67**

entry	R	product	conversion	yield (%)	**3.66**:**3.67**[b]	ee[b] (%)
1	hexyl	**3.66e**	full	72	98:2	98 (+)
2	*iso* pentyl	**3.66f**	full	64	98:2	99 (+)
3	$BnCH_2$	**3.66g**	47%	30	93:7	88 (+)

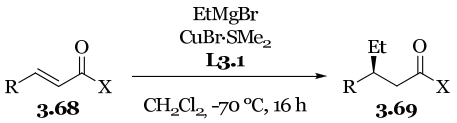
[a] Conditions: a solution of **3.36c** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **3.36c**). [b] Ratio **3.66**: **3.67** and ee's were determined by chiral GC or HPLC.

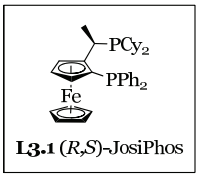
tert butyl sorbate a similar intermediate is destabilized by the bulkiness of the *tert* butyl group. Alternatively, the higher conversion for the 1,6-addition can possibly be attributed to the intrinsic higher reactivity of *tert* butyl sorbate as Michael acceptor, as was concluded from the IR spectroscopy (vide supra).

3.7 Influence of the electron withdrawing group on the 1,6-ACA

For the 1,4-ACA with Grignard reagents to reactive Michael acceptors (i.e. α,β-unsaturated thioesters and ketones) good enantioselectivity is obtained (Table 3.8).[24,26] In contrast for the asymmetric 1,6-addition, the use of more electron-poor Michael acceptors leads to a decrease in both regio- and enantioselectivity (Table 3.9, for further discussion see paragraph 2.6).

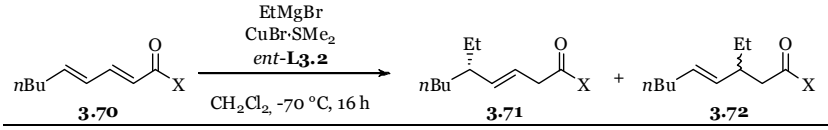
Table 3.8. *Influence of more reactive Michael acceptors on 1,4-ACA.*





entry	X	R	yield (%)	1,4:1,2	ee (%)
1	OMe	pentyl	89	>99:1	88
2	SMe	pentyl	91	>99:1	87
3	Me	*n*Bu	91	96:4	90

Table 3.9. *Influence of more reactive Michael acceptors on 1,6-ACA.*[a]



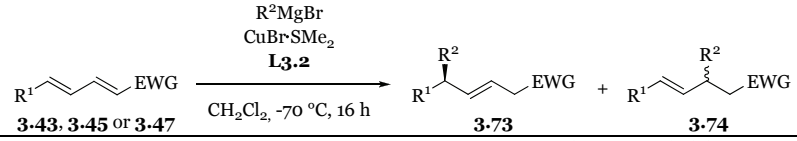
entry	X	yield (%)	**3.71:3.72**[b]	ee[b] (%)
1	OEt	80	99:1	93
2	SEt	58	>95:5[e]	~40
3	Me	~60	63:37	~30

[a] Conditions: **3.70** was added to a solution of RMgBr (3.0 M in Et_2O, 2.0 equiv), (*S*,*R*)-**L3.2** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in **3.70**). [b] Ratio **3.71**:**3.72** and ee's were determined by chiral GC.

Furthermore, when substrates with an electron withdrawing group possessing a possible second coordination site for magnesium (i.e. an additional carbonyl or heteroatom) are used in the asymmetric 1,6-addition it was observed that the products were obtained with negligible ee[27] (Table 3.10). For example the 2-pyridinyl sulfone **3.43** gave the 1,6-addition product **3.73a** in low yield and excellent regioselectivity but with only 2% ee. In contrast, the use of α,β-unsaturated 2-pyridinyl sulfone as substrate in the 1,4-ACA of Grignard reagents using the Cu-TolBINAP catalyst gave good results with respect to yield, regio- and enantioselectivity.[17] Furthermore, the use of oxazolidinone **3.47** gave the 1,6-addition product **3.73b** in reasonable yield and regioselectivity with only 3% ee. Again this is in sharp contrast to the Cu-catalyzed 1,4-addition of EtMgBr to the

corresponding oxazolidinone, which gives reasonable ee (50%) using JosiPhos as ligand (**L3.1**).[24] Finally, the reaction of imidazolinone **3.45** with phenethylmagnesium bromide[viii] gave low yield and only 3% ee of, almost exclusively, the 1,4-addition product **3.73c**. The reversal of regioselectivity for this substrate is unexpected and needs further study. However, the reversal might be explained by a coordination of the Grignard reagent to the imidazole moiety.

Table 3.10. *Reaction of several bisunsaturated Michael acceptors with Grignard reagents.*[a]



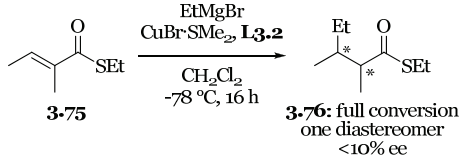
entry	substrate	R^1	EWG	R^2	product	yield	**3.73**:**3.74**[b]	ee[b]
1	**3.43**	*n*Bu	2-pyridinyl sulphone	Et	**3.73a**	26%	98:2	2%
2	**3.47**	Me	oxazolidinone	Et	**3.73b**	64%	75:25	3%
3	**3.45**	Me	2Me-imidazolinone	$BnCH_2$	**3.74c**	34%	<5:>95[c]	2%

[a] Conditions: substrate was added to a solution of RMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in CH_2Cl_2 (0.2 M in substrate). [b] Ratio **3.73**:**3.74** and ee's were determined by chiral GC or HPLC. [c] Ratio **3.73**:**3.74** determined by ^1H NMR.

3.8 Influence of substitution of the olefins on the 1,6-ACA

Me-substitution on either the α- or β-position of the α,β-unsaturated substrates gives inferior results for the 1,4-ACA with Grignard reagents. The α-Me substituted thioester substrate **3.75** gave the 1,4-addition product **3.76** as a single diastereomer with negligible ee using **L3.2** as ligand (Scheme 3.16).[ix] In contrast the 1,4-ACA of EtMgBr to β-Me substituted α,β-unsaturated esters gave no conversion.[x]

Scheme 3.16. *1,4-ACA with an α-Me substituted substrate with Cu-reversed JosiPhos.*



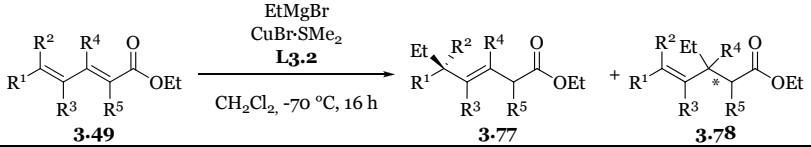
[viii] The reversal of regioselectivity cannot be attributed to the use of phenethylmagnesium bromide. When EtMgBr was used instead of phenethylmagnesium bromide again the 1,4-product was obtained. Unfortunately no separation of the enantiomers was found for this product.

[ix] Unpublished results.

[x] Unpublished results.

In view of the results for Me-substituted substrates in 1,4-ACA, a study of Me-substitution on 1,6-addition substrates might provide information on the similarity of the 1,4-ACA and 1,6-ACA. The 1,6-ACA of α-Me substituted substrate **3.49a** with EtMgBr gave a 1:1 mixture of the two possible diastereomers of the 1,6-addition product in excellent regio- and enantioselectivity (Table 3.11, entry 1). In contrast, β-Me substituted substrate **3.49i** gave low conversion at −70 °C and a mixture of 1,4-addition and 1,6-addition products (entry 2). The γ-Me substituted substrate **3.49b** gave low conversion at −70 °C as well (entry 3). However, when **3.49b** was allowed to react at −60 °C for 2 days, the 1,6-addition product was obtained as a mixture of *E*- and *Z*-isomers in good combined yield and regioselectivity though with low ee (entry 4). This low ee relates to the 1,4-ACA of α-Me substituted α,β-unsaturated thioester **3.76**. Finally, δ-Me substituted substrate **3.49c** gave low conversion to predominantly the 1,4-addition product **3.78c** at −70 °C in 16 h (entry 5), while at −60 °C in 48 h for this substrate slightly higher conversion was obtained to a mixture of 1,4- and 1,6-addition product (entry 6).

Table 3.11. *The influence of substitution of the olefins for 1,6-ACA.*



3.49 **3.77** **3.78**

entry		R1	R2	R3	R4	R5	conversion	yield	**3.77**:**3.78**[b]	ee **3.77**[b]
1	**3.49a**	*n*Bu	H	H	H	Me	94%	83%	99:1	97%
2	**3.49i**	*n*Bu	H	H	Me	H	<25%[c]	19%[d]	nd	nd
3	**3.49b**	Me	H	Me	H	H	~15%[e]	nd[f]	nd[f]	5%[g]
4[h]	**3.49b**	Me	H	Me	H	H	89%	59%	>92:<8	0%
5	**3.49c**	Me	Me	H	H	H	~25%[i]	nd	5:95	–[j]
6[h]	**3.49c**	Me	Me	H	H	H	~40%[k]	nd	57:43	–[l]

[a] Conditions: a solution of **3.49** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **3.49**). [b] Ratio **3.77**:**3.78** and ee's were determined by chiral GC or HPLC. [c] ~55% of **3.49i** was recovered. [d] Mixture of products with fragmentation corresponding to 1,6- and 1,4-addition products. [e] ~55% of **3.49b** was recovered. [f] Overlap of **3.49b** and **3.78b** on chiral GC did not allow determination of these ratios. [g] Ee for the *Z*-1,6-addition product. [h] Reaction time: 48 h, reaction temperature: −60 °C. [i] ~40% of **3.49c** was recovered. [j] Ee of **3.78c**: 27%. [k] ~60% of **3.49c** was recovered. [l] Ee of **3.78c**: 35%.

3.9 Influence of olefin geometry on the 1,6-ACA

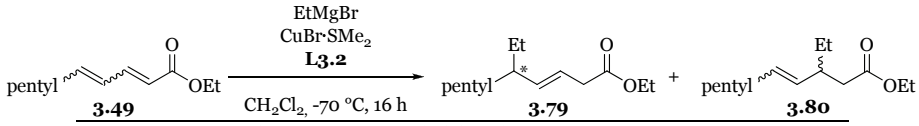
As described in paragraph 3.1, for the 1,4-ACA of EtMgBr to the *E*- or *Z*-methyl cinnamate (Table 3.3, page 83, entry 6 and 7) the 1,4-addition products are obtained in either excellent ee (98% *R*-enantiomer from *E*-isomer) or modest ee (53% *S*-enantiomer from *Z*-isomer).[2] Since *Z*-*E* isomerization of *Z*-methyl cinnamate was observed during the reaction (Table 3.3, entry 8), it was concluded that the difference in ee for the *E*- or *Z*-olefin was due to this isomerization.[2] Furthermore, it was concluded that the rate determining step of the mechanism follows after the formation of the σ-Cu^{III} intermediate **3.12** (Scheme 3.4, page 84).[2]

The study of the olefin geometry on the enantioselectivity for the 1,6-ACA might give additional insight in the mechanism of this reaction (Table 3.12). First, the influence of the geometry of the terminal olefin on the enantioselectivity of the reaction was studied. Cu-(*R*,*S*)-**L3.2**-catalyzed 1,6-ACA of EtMgBr to 2*E*,4*E*-**3.49d** gave the 1,6-addition product **3.79** in good yield and excellent regio- and enantioselectivity (entry 1). The opposite enantiomer of product **3.79** was obtained with a similar ee when 2*E*,4*Z*-**3.49j**[xi] was used (entry 2). The formation of the opposite enantiomer of the 1,6-product with similar ee indicates that no Z,E-isomerization of the C4-olefin takes place during the reaction. Furthermore, the formation of the enantiomers of the 1,6-product **3.79** indicates that the rate determining step of the mechanism is not the reductive elimination from σ-Cu^{III} intermediate **3.31** (Scheme 3.7, page 87) to form the product, but instead is one of the earlier steps in the mechanism.

For the 1,6-ACA of EtMgBr to 2*Z*,4*E*-**3.49g** and 2*Z*,4*Z*-**3.49h**[xii] the reaction proceeds with lower enantioselectivity (Table 3.12, entry 3 and 4). The lower enantioselectivity might be explained by either a different angle between the reaction site and the ester moiety, resulting in different π-complexation and thus a different steric environment in the enantiodetermining step, or alternatively by isomerization of one of the olefins during the reaction.

The ee is higher for the 1,6-ACA product when 2*Z*,4*Z*-**3.49h** is used compared to the use of 2*Z*,4*E*-**3.49g**. With respect to the complete reversal of the ee for the products of the 1,6-ACA to 2*E*,4*E*-**3.49d** and 2*E*,4*Z*-**3.49j** this difference in stereoinduction is unexpected. The different amount of enantioselectivity might indicate an *Z*,*E*-isomerization of the internal olefin for which the rate is dependent on the olefin geometry of the C4-olefin or alternative an *Z*,*E*-isomerization of the terminal olefin which is dependent on the olefin geometry of the C2-olefin. Furthermore, since a mixture of substrates was used to calculate the ee for the

Table 3.12. *Influence of the olefin geometry on 1,6-ACA.*[a]



entry	substrate	yield (%)	**3.79**:**3.80** [b]	ee[b] (%)
1	2*E*,4*E*-**3.49d**	80	98:2	98 (*R*)
2[c]	2*E*,4*Z*-**3.49j**	73	98:2	99 (*S*)[d]
3	2*Z*,4*E*-**3.49g**	71	99:1	3 (*S*)
4[e]	2*Z*,4*Z*-**3.49h**	72	99:1	30 (*R*)

[a] Conditions: a solution of **3.49** in CH_2Cl_2 was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **3.49**). [b] Ratio **3.79**:**3.80** and ee's were determined by chiral GC or HPLC. [c] Reaction was performed on a mixture of 1.0:0.1 2*E*,4*Z*-**3.49j**:2*E*,4saturated-**3.57**. [d] The enantiomer of the catalyst was used and the enantiomer of the product was obtained. [e] Reaction was performed on a mixture of 1.2:1.0:0.8 2*Z*,4*E*-**3.49g**:2*Z*,4*Z*-**3.49h**:2*E*,4*E*-**3.49d** and the ee for exclusively the 2*Z*,4*Z*-**3.49h** was calculated.

[xi] This reaction was performed on a mixture of 2*E*,4*Z*-**3.49j** and 2*E*,4saturated-**3.57**.

[xii] This reaction was performed on a mixture of 2*Z*,4*E*-**3.49g**, 2*Z*,4*Z*-**3.49h** and traces of 2*E*,4*E*-**3.49d**. The enantioselectivity for the reaction was calculated from the observed enantioselectivity of this reaction.

product of the 1,6-ACA to 2*Z*,4*Z*-**3.49h**, possible aggregation complexes of the substrates in the reaction leading to the difference in enantioselectivity cannot be excluded.

Further experiments with pure 2*E*,4*Z*-**3.49j** and pure 2*Z*,4*Z*-**3.49h**, as well as a study of the possible *Z*,*E*-isomerization over time for all enantiomers, are required to explain the results described in this paragraph.

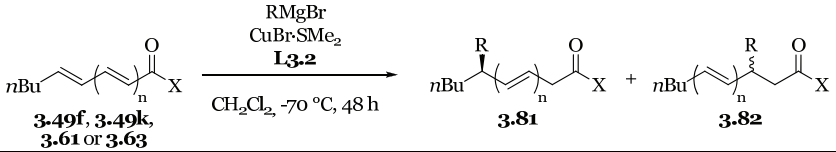
3.10 1,8-ACA and 1,10-ACA

Since the 1,6-ACA with Grignard reagents to α,β,γ,δ-bisunsaturated esters and the 1,6-ACA with MeMgBr to thioesters proceeds with high regio- and enantioselectivity, the 1,8-ACA and 1,10-ACA to multiple unsaturated esters and thioesters was explored. For the ACA of EtMgBr to 1,8-addition ester substrate **3.49f** the reaction turned out to be slow and full conversion was obtained in 48 h (Table 3.13, entry 1). This reaction yielded a mixture of 1,8- and 1,4-products in reasonable yield and the 1,8-addition product was obtained in 7% ee.[xiii] Also ACA of MeMgBr to 1,8-ACA thioester substrate **3.61** was slow and with an increased amount of catalyst (7.5 mol%) the 1,8-addition product was obtained with good yield, regio- and enantioselectivity in 48 h with almost full conversion (entry 2).

The 1,10-ACA turned out to be even slower than the 1,8-ACA. The ACA to ester **3.49k** gave 85% conversion in 48 h and a mixture of predominantly 1,10- and 1,4-product (entry 3). Furthermore, traces of either a 1,8- or 1,6-product were obtained. The 1,10-product was obtained in similar ee compared to the product of the 1,8-ACA to **3.49f**. Finally, a mixture of 1,10-product and 1,4-product was obtained from the addition of MeMgBr to thioester **3.63** (entry 4). The higher amount of catalyst (10 mol%) used for this reaction did not lead to full conversion. The 1,10-addition product was obtained with 45% ee.

A distinct difference between the enantioselectivity of the extended conjugate addition of EtMgBr to multiple unsaturated esters and the addition of MeMgBr to multiple unsaturated thioesters was found. This difference can possibly be

Table 3.13. *1,8-ACA and 1,10-ACA.*[a]



entry	substrate	n	X	R	conversion	yield	**3.81**:**3.82**[b]	ee **3.81**[b]
1	**3.49f**	2	OEt	Et	full	47%	63:29	7%
2[c]	**3.61**	2	SEt	Me	92%	63%	86:14	73%
3	**3.49k**	3	OEt	Et	85%	22%	49:43	12%
4[d]	**3.63**	3	SEt	Me	82%	44%	59:41	45%

[a] Conditions: substrate was added to a solution of RMgBr (3.0 M in Et_2O, 2.0 equiv), (*R*,*S*)-**L3.2** (5.25 mol%) and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in substrate). [b] Ratio **3.81**:**3.82** and ee's were determined by chiral GC. [c] (*R*,*S*)-**L3.2** (7.88 mol%) and CuBr·SMe_2 (7.5 mol%) were used. [d] (*R*,*S*)-**L3.2** (10.5 mol%) and CuBr·SMe_2 (10 mol%) were used.

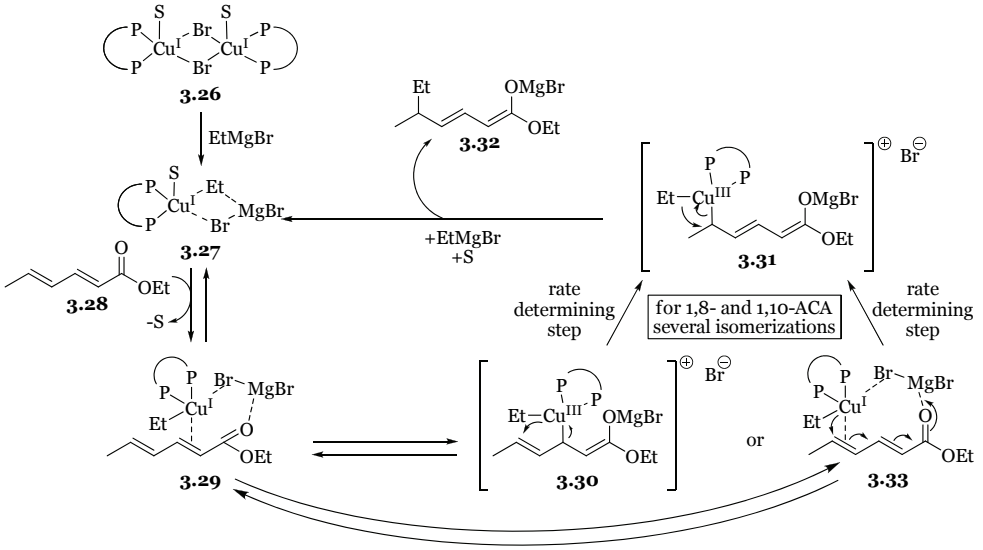
[xiii] No separation on chiral GC was found for the 1,4-ACA product.

attributed to the difference in reactivity of the Grignard reagent, which might cause a change in the enantiodetermining step of the extended conjugate additions. Furthermore, a clear trend with respect to the enantioselectivity for the addition of MeMgBr to the remote olefin of the thioesters was observed; the further away the new stereogenic centre is from the (thio)ester moiety, the lower the observed enantioselectivity is. Finally, another trend is the increased formation of 1,4-product for the more extended conjugated systems (i.e. the 1,10-addition substrates).

3.11 On the mechanism of asymmetric extended conjugate additions

With the results described in this chapter, the mechanism in Scheme 3.17 can be proposed for the asymmetric conjugate additions of Grignard reagents with Cu-reversed JosiPhos as catalyst. The results support a mechanism for the asymmetric extended conjugate addition in which the internal olefin is involved in one of the first steps. In particular, the influence of the size of the ester as well as the presence of the α-Me substitution on the reaction rate indicate that in the rate determining step the steric bulk around the ester has an influence on the energy barrier of this step. Furthermore, the low conversion for the 1,6-ACA to the substrate with β-Me substitution indicates that interaction with the β-position is required for the formation of the 1,6-addition product.

Scheme 3.17. *Proposal for the mechanism of asymmetric extended conjugate addition with Grignard reagents.*



Used abbreviations: S=solvent (in this case CH_2Cl_2). P-P= reversed JosiPhos ligand.
Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^I-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules. 3) *Trans* or *cis* relationship with respect to the distinct phosphor atoms of the ligand is not taken into account in the depiction of this mechanism.

A mechanism involving Cu-migration is supported by the addition of the alkyl group to either the terminus of the conjugated system (i.e. 1,8- or 1,10-addition) or to the β-position (i.e. 1,4-addition) and the lower reaction rates for 1,8-ACA and 1,10-ACA compared to 1,6-ACA. In analogy with the proposed mechanism by Nakamura and co-workers,[9] and in view of the absence of *Z-E* isomerization for the C4 olefin and the observed regioselectivity for 1,8- and 1,10-ACA, the Cu-migration from the 4-position to the 6-position can be proposed as rate determining step.

Whether or not the mechanism for extended conjugate addition involves multiple σ-Cu^{III} intermediates needs further investigation. Especially, further studies on the influence of the olefin geometry on the 1,6-ACA and possible *Z-E* isomerization of the 2*Z*,4*Z*- and 2*Z*,4*E*-α,β,γ,δ-bisunsaturated esters in the reaction together with molecular modelling studies might give more information on these intermediates.

3.12 On the stereochemical pathway of asymmetric extended conjugate additions

Two trends concerning the stereochemical discrimination of the 1,6-ACA can be discerned from the results in this chapter. First of all, the more bulk present around the ester moiety, either provided by the alkoxy group or the α-Me substitution, the higher is the enantioselectivity observed for the 1,6-ACA. The inverse trend for the influence of the size of the ester moiety for 1,6-ACA, compared to 1,4-ACA, hints that the stereochemistry is not fixed in the intermediate when the catalyst is coordinated to the internal olefin. However, a possible additional coordination of the terminal olefin to the catalyst, when the catalyst is coordinated to the internal olefin, cannot be excluded to account for this inversed trend. Furthermore, in view of the results for asymmetric 1,6-addition with a diversity of electron withdrawing groups we postulate that mono-coordination of the magnesium ion allows the 1,6-ACA to proceed with high enantioselectivity, while in case of double coordination of the magnesium all enantiodiscrimination is lost.

For the 1,8-ACA and 1,10-ACA due to the decrease of enantioselectivity associated with the larger distance between the terminal olefin and the ester, the enantiodiscrimination is possibly governed in the formation of one of the earlier intermediates (most likely in an intermediate involving coordination of the catalyst to the C4-olefin) and further transferred (memorized) along the conjugated system with slight loss of enantioselectivity (Table 3.13, page 98). However, a possible cyclic intermediate involving the ligand bound to the terminal olefin and the ester moiety cannot be excluded.

3.13 Conclusions

Although there are similarities between the 1,4-ACA and 1,6-ACA many differences have been encountered as well. The similarities comprise mainly the influence of the substitution pattern of the employed substrates on the conjugate additions. The main differences are that the enantioselectivity of the 1,4-ACA and 1,6-ACA is influenced differently by the bulk of the ester moiety. Thus the

stereochemistry is not induced via a similar intermediate involving coordination of the catalyst to the internal olefin for both 1,4-ACA and 1,6-ACA. Furthermore, although 1,4-ACA to more reactive Michael acceptors proceeds with good regio- and enantioselectivity the 1,6-ACA to α,β,γ,δ-bisunsaturated ketones gives poor regio- and enantioselectivity.

Although the results described in this chapter can only give a preliminary model for the mechanism of the asymmetric extended conjugate additions and can only give hints for a model for the induction of stereochemistry in 1,6-ACA, the observed differences between 1,4-ACA and 1,6-ACA are well suited for further studies using molecular modelling.

3.14 Perspective and outlook

The studies described in this chapter give some insight in the mechanism of 1,6-ACA. However, further studies are definitely needed to gain a better understanding of the mechanism of this reaction. Especially the identification of intermediates is highly warranted to increase the understanding of the mechanism. Possibly the lower reaction rate of 1,8-ACA and 1,10-ACA will allow the identification of intermediates by NMR-studies.

Without identification of intermediates a study of the kinetics of the 1,6-ACA, including determination of the rate determining step by kinetic isotope effects,[9] which requires combined ^{13}C NMR spectroscopy and molecular modeling studies, might give some information into the reaction mechanism.

Furthermore, although bromide is expected to play a similar role as in the 1,4-ACA,[2] i.e. this halide is required for high enantioselectivity, studies should be performed on the influence of the halide in the Cu-source and Grignard reagent for 1,6-ACA. Finally, the studies on the influence of the olefin geometry on 1,6-ACA should be extended.[xiv]

3.15 Acknowledgment

Anne Meuwese is acknowledged for the results concerning the 1,6-addition of alkyl Grignard reagents to *tert* butyl sorbate described in paragraph 3.6. Dr. Wesley Browne is acknowledged for fruitful discussions on the IR-experiments described in paragraph 3.6. Dr. Alena Rudolph is acknowledged for the synthesis of substrates **3.49g**, **3.49h** and **3.49i**. Finally, Dr. Marco Bouwkamp is acknowledged for fruitful discussions on the mechanism of 1,6-addition.

[xiv] For discussion of further studies on the 1,4-ACA, see paragraph 7.7.

3.16 Experimental section

General procedures: All reactions under a N_2 atmosphere were conducted using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere prior to use. Et_2O was distilled from Na using benzophenone as indicator under a N_2 atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under N_2 prior to use. CuBr•SMe_2 was purchased from Sigma-Aldrich. (–)-(*R*,*S*)-reversed Josiphos and (+)-(*S*,*R*)-reversed Josiphos were purchased from Sigma-Aldrich. Grignard reagents were purchased from Sigma-Aldrich (EtMgBr and hexylMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et_2O following standard procedures. Grignard reagents were titrated using *s*BuOH and catalytic amounts of 1,10-phenanthroline before use.
Sorbic acid, oxalyl chloride (2 M solution in CH_2Cl_2), NaH (60% dispersion in mineral oil), diethyl (2-oxopropyl)phosphonate, oxazolidin-2-one, 2-chloro-1-methylpyridinium iodide, triethyl phosphonopropionate, catecholborane, *N*,*N*-dimethylacetamide, palladium(II) acetate, ethyl crotonate, triethyl phosphonoacetate, (*E*)-oct-2-enal, oct-2-ynal, Lindlar catalyst, ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate, 18-crown-6, *t*BuOK, (2*E*,4*E*)-nona-2,4-dienal (85% technical grade) and DIBAL-H (1.0 M in CH_2Cl_2) were purchased from Sigma-Aldrich. DMF, *E*-hept-2-enal, *n*BuLi, 1-hexyne, *E*-2-methylbut-2-enal, 3-methylbut-2-enal and quinoline were purchased from ACROS. MeOH and *i*PrOH were purchased from Lab-Scan. *t*BuOH and Na_2CO_3 was purchased from Boom. 1-Methyl-1H-imidazole was purchased from Janssen Chimica. Triethylamine was purchased from Merck. Pinacol was purchased from Fluka.
S-ethyl 2-(triphenylphosphoranylidene)ethanethioate (**3.38**) was prepared as described in ref 15. IBX was prepared as described in ref 28.
Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F_{254} silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Ee and regioselectivities were determined by chiral GC (CP-Chiraldex-B-PM (30 m x 0.25 mm)) using flame ionization detection or HPLC analysis ((*R*,*R*)-Whelk-01, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm; chiralcel OD-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 215 nm; chiralcel OJ-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 275 nm) (in comparison to authentic samples of racemates of the products). Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ= 7.26 for hydrogen atoms, δ= 77.16 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a FTMS Orbitrap FischerScientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). IR spectra were recorded Perkin on an Elmer Spectrum 400 equipped with a UATR attachment and liquid N_2 cooled MCT detector.

Influence of the ester size:
General procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β,γ,δ-bisunsaturated carboxylic acids:[14]
In a dried two necked flask equipped with septum and stirring bar under a N_2 atmosphere, sorbic acid (1 equiv) was dissolved in CH_2Cl_2 (4.0 mL/mmol substrate) and DMF (1 equiv) was added. Then oxalyl chloride (3 equiv, 2 M solution in CH_2Cl_2) was added slowly (over 30 min) with the formation of CO and CO_2 gas. After stirring for 1 h (after addition) at rt the alcohol (6 equiv) was added and the reaction the

mixture was stirred for an additional 4 h. The reaction mixture was quenched with a saturated aq $NaHCO_3$ solution (4 mL/mmol substrate) and the layers were separated. The organic layer was washed with the aq $NaHCO_3$ solution (2x 4 mL/mmol substrate) and the resulting combined aqueous layers were washed with CH_2Cl_2 (4 mL/mmol substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:49 Et_2O:pentane) yielded the product as a colorless oil.

2*E*,4*E*-methyl hexa-2,4-dienoate (**3.36a**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β,γ,δ-bisunsaturated carboxylic acids using MeOH.
[5.0 mmol scale, 77% yield, colorless oil]
Data were in accordance to those given in ref 29; additional data: MS *m/z* 126 (M^+, 49), 111 (M^+-Me, 100), 95 (M^+-OMe, 59), 67 (C_4H_3O, 85); HRMS calcd. for $C_7H_{10}O_2Na$ 149.0578, found 149.0578.

2*E*,4*E*-*iso*-propyl hexa-2,4-dienoate (**3.36b**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β,γ,δ-bisunsaturated carboxylic acids using *i*PrOH.
[5.0 mmol scale, 83% yield, colorless oil]
^{1}H NMR δ 7.16 (dd, *J*= 15.3 Hz, 9.8 Hz, 1H), 6.18-5.98 (m, 2H), 5.68 (d, *J*= 15.4 Hz, 1H), 5.08-4.94 (m, 1H), 1.78 (d, *J*= 6.0 Hz, 3H), 1.20 (dd, *J*= 6.3 Hz, 1.5 Hz, 6H); ^{13}C NMR δ 166.74 (C), 144.58 (CH), 138.87 (CH), 129.84 (CH), 119.62 (CH), 67.35 (CH), 21.91 (CH_3), 18.59 (CH_3); MS *m/z* 154 (M^+, 21), 112 (M^+-*i*Pr+H, 40), 97 ($C_5H_5O_2$, 100), 95 (M^+-O*i*Pr, 93), 67 (C_4H_3O, 69); HRMS calcd. for $C_9H_{14}O_2Na$ 177.0886, found 177.0881.

2*E*,4*E*-*tert*-butyl hexa-2,4-dienoate (**3.36c**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β,γ,δ-bisunsaturated carboxylic acids using *t*BuOH.
[4.5 mmol scale, 83% yield, colorless oil]
Data were in accordance to those given in ref 30; additional data: ^{13}C NMR δ 166.69 (C), 143.90 (CH), 138.41 (CH), 129.88 (CH), 121.05 (CH), 80.01 (C), 28.24 (CH_3), 18.63 (CH_3); MS *m/z* 168 (M^+, 36), 113 (49), 112 (M^+-*t*Bu+H, 40), 97 ($C_5H_5O_2$, 85), 95 (M^+-O*t*Bu, 76), 67 (C_4H_3O, 56), 57 (C_2HO_2, 100); HRMS calcd. for $C_{10}H_{16}O_2$ 168.1151, found 168.1150.

General procedure for the enantioselective 1,6-conjugate addition:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuBr•SMe_2 (5.0 mol%) and (*R*,*S*)-reversed JosiPhos (5.25 mol%) were dissolved in anhydrous CH_2Cl_2 (4 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to −70 °C and the Grignard reagent (2.0 equiv) was added. After stirring for an additional 10 min, a solution of the substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 1.0 mL/ mmol substrate) was added with syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at −70 °C and subsequently EtOH (0.2 mL/mmol substrate) and an aq NH_4Cl-solution (1 M, 1.0 mL/mmol substrate) were added. The mixture was warmed to rt and an additional 10 mL/mmol substrate of the NH_4Cl-solution and 10 mL/mmol substrate of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2 x 10 mL/mmol substrate), the combined organic extracts were dried and in view of the volatility carefully concentrated to a yellow oil. Flash column chromatography (3:97 Et_2O:pentane) yielded the product as a colorless[xv] oil.

(*S*,*E*)-methyl 5-methylhept-3-enoate (**3.66a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-methyl hexa-2,4-dienoate and EtMgBr.
[0.5 mmol scale, 64% yield,[xvi] 75% ee, 1,6:1,4= >99:1, colorless oil]

xv Occasionally the product was polluted by traces of a yellow colored side product undetectable by GC/MS or NMR.
xvi The low yield can be explained by either volatility or a substantial degradation of methyl sorbate under reaction conditions.

$[\alpha]_D^{20}$= +14.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.55-5.34 (m, 2H), 3.66 (s, 3H), 3.02 (d, *J*= 5.9 Hz, 2H), 2.02 (dt, *J*= 13.5 Hz, 6.8 Hz, 1H), 1.28 (p, *J*= 7.3 Hz, 2H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.83 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 172.77 (C), 140.55 (CH), 119.97 (CH), 51.80 (CH_3), 38.39 (CH), 38.05 (CH_2), 29.66 (CH_2), 20.04 (CH_2), 11.76 (CH_3); MS *m/z* 156 (M^+, 5), 85 ($C_4H_5O_2$, 100), 82 (C_5H_6O, 80), 67 (C_4H_3O, 45), 59 ($C_2H_3O_2$, 44), 55 (C_3H_3O, 95); HRMS calcd. for $C_9H_{16}O_2Na$ 179.1043, found 179.1039; Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[31,xvii] column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 70 min, 60 °C to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 81.5 (major), 82.0 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 140 min, retention times (min): 112.6 (1,4-product), 119.6 (1,6-product).

(*S*,*E*)-*iso*-propyl 5-methylhept-3-enoate (**3.66b**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-*iso*-propyl hexa-2,4-dienoate and EtMgBr.
[0.5 mmol scale, 82% yield, 97% ee, 1,6:1,4= 99:1, colorless oil]
$[\alpha]_D^{20}$= +13.7 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.52-5.34 (m, 2H), 5.05-4.93 (m, 1H), 2.96 (d, *J*= 6.6 Hz, 2H), 2.01 (dt, *J*= 13.5 Hz, 6.7 Hz, 1H), 1.34-1.15 (m, 8H), 0.95 (dd, *J*= 6.7 Hz, 1.6 Hz, 3H), 0.83 (td, *J*= 7.3 Hz, 1.4 Hz, 3H); ^{13}C NMR δ 171.89 (C), 140.30 (CH), 120.34 (CH), 67.81 (CH), 38.62 (CH_2), 38.45 (CH), 29.69 (CH_2), 21.92 (CH_3), 20.16 (CH_3), 11.79 (CH_3); MS *m/z* 184 (M^+, 2), 142 (M^+-*i*Pr+H, 21), 124 ($C_8H_{12}O$, 31), 113 (22), 97 (M^+-CO_2*i*Pr, 44), 82 (C_6H_{10}, 52), 67 (C_4H_3O, 22), 55 (C_3H_3O, 100); HRMS calcd. for $C_{11}H_{20}O_2Na$ 207.1356, found 207.1351; Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[31,xvii] column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 70 min, 60 °C to 160 °C in 10 min, 160 °C for 4 min; retention times (min): 81.3 (major), 82.1 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 140 min, 60 °C to 160 °C in 10 min, retention times (min): 149.0 (1,4-product, minor), 149.1 (1,4-product, major), 149.9 (1,6-product).

(*S*,*E*)-*tert*-butyl 5-methylhept-3-enoate (**3.66c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-*tert*-butyl hexa-2,4-dienoate and EtMgBr.
[0.5 mmol scale, 88% yield, 98% ee, 1,6:1,4= 98:2, colorless oil]
$[\alpha]_D^{20}$= +15.3 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.56-5.30 (m, 2H), 2.90 (d, *J*= 6.4 Hz, 2H), 2.01 (dt, *J*= 13.6 Hz, 6.8 Hz, 1H), 1.43 (s, 9H), 1.37-1.20 (m, 2H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.83 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 171.72 (C), 140.00 (CH), 120.74 (CH), 80.37 (C), 39.53 (CH_2), 38.45 (CH), 29.71 (CH_2), 28.20 (CH_3), 20.19 (CH_3), 11.79 (CH_3); MS *m/z* 198 (M^+, 1), 142 (M^+-*t*Bu+H, 15), 97 (M^+-CO_2*t*Bu, 17), 57 (C_4H_9, 100); HRMS (APCI+) calcd. for $C_{12}H_{22}O_2Na$ 221.1512, found 251.1503; Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[31,xvii] column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 70 min, 60 °C to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 81.6 (major), 82.1 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 140 min, 60 °C to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 150.6 (1,4-product, minor), 150.7 (1,4-product, major), 151.2 (1,6-product).

(*S*,*E*)-*tert*-butyl 5-methylundec-3-enoate (**3.66e**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-*tert*-butyl hexa-2,4-dienoate and hexylMgBr.
[0.5 mmol, 72% yield, 98% ee, regioselectivity 1,6:1,4= 98:2, colorless oil]
$[\alpha]_D^{20}$= +9.6 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ ^{1}H NMR δ ^{1}H 5.50 – 5.33 (m, 2H), 2.91 (d, *J*= 6.1 Hz, 2H), 2.15-2.04 (m, 1H), 1.44 (s, 9H), 1.32-1.19 (m, 10H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.87 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 171.78 (C), 140.36 (CH), 120.48 (CH), 80.41 (C), 39.57 (CH_2), 37.06 (CH_2), 36.81 (CH), 32.03 (CH_2), 29.57 (CH_2), 28.22 (CH_3), 27.36 (CH_2), 22.82 (CH_2), 20.67 (CH_3), 14.25 (CH_3); MS *m/z* 254 (M^+, 1), 128 ($C_7H_{12}O_2$, 30), 57 (C_4H_9, 100); HRMS calcd. for $C_{16}H_{31}O_2$ 255.2318, found 255.2318. Regio- and enantioselectivity were determined by conversion into the ethyl ester[32] and subsequent

[xvii] 2-methylbutanoic acid was obtained by Ru-catalysed $NaIO_4$-oxidation as described in: P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936-3938.

chiral GC analysis, column: Chiraldex-B-PM, 80°C, retention times (min): 79.3 (1,4-product), 98.0 (1,6-product, minor), 105.3 (1,6-product, major).

(*S,E*)-*tert*-butyl 5,8-dimethylnon-3-enoate (**3.66f**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-*tert*-butyl hexa-2,4-dienoate and *iso* pentylMgBr.
[64% yield, 99% ee, regioselectivity 1,6:1,4= 98:2, colorless oil]
$[\alpha]_D^{20}$= +7.0 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 5.52-5.32 (m, 2H), 2.91 (d, *J*= 6.0 Hz, 2H), 2.14-1.99 (m, 1H), 1.56-1.39 (m, 10H), 1.25 (ddd, *J*= 12.6 Hz, 7.1 Hz, 2.0 Hz, 2H), 1.19-1.07 (m, 2H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.85 (dd, *J*= 6.6 Hz, 0.6 Hz, 6H); ^{13}C NMR δ 171.77 (C), 140.37 (CH), 120.51 (CH), 80.42 (C), 39.58 (CH_2), 37.08 (CH), 36.68 (CH_2), 34.81 (CH_2), 28.28 (CH), 28.22 (CH_3), 22.85 (CH_3), 22.76 (CH_3), 20.71 (CH_3); MS *m/z* 240 (M^+, 1), 128 ($C_7H_{12}O_2$, 35), 57 (C_4H_9, 100); HRMS calcd. for $C_{15}H_{29}O_2$ 241.2162, found 241.2162. Regio- and enantioselectivity were determined by conversion into the ethyl ester[32] and subsequent chiral GC analysis, column: Chiraldex-B-PM, 90°C, retention times (min): 121.9 (1,4-product, major), 129.1 (1,4-product, minor), 138.3 (1,6-product, minor), 139.7 (1,6-product, major).

(*S,E*)-*tert*-butyl 5-methyl-7-phenylhept-3-enoate (**3.66g**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-*tert*-butyl hexa-2,4-dienoate and phenethylMgBr; reaction time: 48 h.
[47% conversion, 30% yield, 88% *ee*, regioselectivity 1,6:1,4= 93:7, colorless oil]
$[\alpha]_D^{20}$= +6.3 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.31-7.13 (m, 5H), 5.58-5.41 (m, 2H), 2.97 (d, *J*= 6.6 Hz, 2H), 2.63-2.53 (m, 2H), 2.24-2.14 (m, 1H), 1.67-1.58 (m, 2H), 1.47 (s, 9H), 1.04 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 171.69 (C), 142.88 (C), 139.76 (CH), 128.54 (CH), 128.38 (CH), 125.71 (CH), 121.34 (CH), 80.53 (C), 39.57 (CH_2), 38.78 (CH_2), 36.47 (CH), 33.72 (CH_2), 28.24 (CH_3), 20.78 (CH_3); MS *m/z* 274 (M^+, 1), 218 (M^+-*t*Bu+H, 32), 131 ($C_{10}H_{11}$, 43), 104 (C_8H_8 33), 191 (C_7H_7, 51), 57 (C_4H_9, 100); HRMS calcd. for $C_{18}H_{26}O_2Na$ 297.1825, found 297.1827; Ee was determined by chiral HPLC analysis, column: (*R,R*)-Whelk-01, (99.9:0.1 heptane:*i*PrOH); retention times (min): 17.3 (major peak, 1,4-addition product), 16.8 (minor peak, 1,4-addition product), 19.1 (*S*-enantiomer, 1,6-addition product), 19.1 (*S*-enantiomer, 1,6-addition product).

Influence of the electron withdrawing group:
(2*E*,4*E*)-S-ethyl nona-2,4-dienethioate (**3.39**) was prepared according the procedure in ref 26a (procedure D; the reaction of aldehydes with $Ph_3PCHCOSEt$, 24 h reaction time) using *E*-hept-2-enal.
[14.9 mmol scale, 61% yield, colorless oil]
^{1}H NMR δ 7.16 (dd, *J*= 15.2 Hz, 10.1 Hz, 1H), 6.22-6.09 (m, 2H), 6.05 (d, *J*= 15.2 Hz, 1H), 2.93 (*J*= 7.4 Hz, 2H), 2.16 (dd, *J*= 13.9 Hz, 6.7 Hz, 2H), 1.39 (dt, *J*= 14.4 Hz, 7.2 Hz, 2H), 1.34-1.29 (m, 2H), 1.26 (td, *J*= 7.4 Hz, 0.5 Hz, 3H), 0.88 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR δ 190.3 (C), 146.6 (CH), 141.1 (CH), 128.4 (CH), 126.6 (CH), 33.1 (CH_2), 31.0 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 15.1 (CH_3), 14.1 (CH_3); MS *m/z* 198 (M^+, 14), 137 (M-SEt, 100), 81 (C_5H_5O, 39); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1083.

3*E*,5*E*-deca-3,5-dien-2-one (**3.41**):[16]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, NaH (60% solution in mineral oil, 2.7 equiv) was vigorously stirred in anhydrous THF (10 mL/mmol aldehyde) and cooled to −20 °C. Diethyl (2-oxopropyl)phosphonate (neat, 3.0 equiv) was added dropwise and the mixture was stirred for 30 min. Subsequently, *E*-hept-2-enal (1.0 equiv) dissolved in anhydrous THF (2.0 mL/mmol aldehyde) was added dropwise. After addition, the solution was stirred for 20 min at −20 °C and was subsequently stirred at rt for 30 min. The reaction mixture was diluted with Et_2O (2 mmol/mmol aldehyde) and the solution was subsequently washed with NH_4Cl (saturated aq solution, 2 mL/mmol aldehyde), Na_2CO_3 (saturated aq solution, 2 mL/mmol aldehyde) and brine (2 mL/mmol aldehyde). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

[7.6 mmol scale, 65% yield, colorless oil]
Colorless oil; data were in accordance with those given in ref 33.

2-(1*E*,3*E*-octa-1,3-dienylsulfonyl)pyridine (**3.43**) was prepared analogous to the general procedure for the synthesis of α,β-unsaturated sulfones in ref 17 using *E*-hept-2-enal.
[3.0 mmol scale, 27% yield (2 steps), slightly yellow viscous oil]
^{1}H NMR δ 8.70 (d, *J*= 4.3 Hz, 1H), 8.06 (d, *J*= 7.8 Hz, 1H), 7.91 (td, *J*= 7.8 Hz, 1.5 Hz, 1H), 7.48 (dd, *J*= 7.1 Hz, 4.9 Hz, 1H), 7.33 (dd, *J*= 14.9 Hz, 10.7 Hz, 1H), 6.45 (d, *J*= 14.9 Hz, 1H), 6.32-6.22 (m, 1H), 6.15 (dd, *J*= 15.1 Hz, 10.8 Hz, 1H), 2.17 (q, *J*= 7.0 Hz, 2H), 1.46-1.21 (m, 4H), 0.87 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR δ 158.92 (C), 150.42 (CH), 148.78 (CH), 145.75 (CH), 138.23 (CH), 127.05 (CH), 126.28 (CH), 124.73 (CH), 121.84 (CH), 32.89 (CH_2), 30.64 (CH_2), 22.32 (CH_2), 13.94 (CH_3); MS *m/z* 251 (M^+, 1), 130 ($C_5H_6O_2S$, 100), 80 (C_6H_8, 44), 79 (38), 78 (C_5H_5N, 29); HRMS calcd. for $C_{13}H_{17}NO_2SNa$ 274.0886, found 274.0868.

2*E*,4*E*-1-(1-methyl-1H-imidazol-2-yl)hexa-2,4-dien-1-one (**3.45**):[18]
In a two necked flask equipped with septum and stirring bar under a N_2 atmosphere, 1-methyl-1H-imidazole (2.2 equiv) was dissolved in anhydrous THF (4.0 mL/mmol substrate) and the flask was cooled to −78 °C and stirred for 30 min. Then *n*BuLi (2.0 equiv, 1.6 M in hexanes) was added drop wise (in 30 min) and stirred for 5 min after addition. Then the reaction mixture was subsequently allowed to warm to rt in 30 min, cooled down again to −78 °C and stirred for 20 min. A solution of sorbic acid (1.0 equiv) in anhydrous THF (0.5 mL/mmol substrate) was added and the reaction mixture was stirred for 10 min after addition. Then the reaction mixture was allowed to warm up to rt in 40 min. The reaction mixture was slowly quenched with a saturated aq $NaHCO_3$ solution (1 mL/mmol substrate), EtOAc (2 mL/mmol substrate) was added and the layers were seperated. The aquous layer was washed with EtOAc (2x 4 mL/mmol substrate). The combined organic extracts were dried and carefully concentrated to a brown solid. Flash column chromatography (1:1 Et_2O:pentane) yielded the product.

[20 mmol scale, 38% yield, white solid, mp: 88.1-88.4 °C]
^{1}H NMR δ 7.35-7.20 (m, 2H), 7.03 (d, *J*= 2.8 Hz, 1H), 6.91 (d, *J*= 2.7 Hz, 1H), 6.27-6.05 (m, 2H), 3.91 (d, *J*= 3.6 Hz, 3H), 1.76 (dd, *J*= 6.4 Hz, 2.4 Hz, 3H); ^{13}C NMR δ 180.92 (C), 143.94 (C), 143.75 (CH), 140.87 (CH), 130.67 (CH), 129.01 (CH), 126.96 (CH), 124.17 (CH), 36.19 (CH_3), 18.86 (CH_3); MS *m/z* 176 (M^+, 29), 161 (M^+-Me, 60), 147 ($C_8H_6N_2O$, 45), 133 ($C_7H_5N_2O$, 100), 82 ($C_4H_6N_2$, 53); HRMS calcd. for $C_{10}H_{13}N_2O$ 177.1022, found 177.1020; Anal. Calc. for $C_{10}H_{12}N_2O$: C, 68.17; H, 6.90; N, 15.91, Found: C, 68.03, H, 6.85; N, 15.86.

3-2*E*,4*E*-hexa-2,4-dienoyloxazolidin-2-one (**3.47**) was prepared analogous to the general coupling procedure (as illustrated for 3-(*E*-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one 7) in ref 19 using sorbic acid and oxazolidin-2-one; Flash column chromatography (1:1 Et_2O:pentane) yielded the product.
[5.0 mmol scale, 17% yield, white solid, mp: 119.7-119.8 °C]
^{1}H NMR δ 7.42 (dd, *J*= 15.0, 10.5 Hz, 1H), 7.17 (d, *J*= 15.1 Hz, 1H), 6.44-6.10 (m, 2H), 4.39 (t, *J*= 8.0 Hz, 2H), 4.05 (t, *J*= 8.0 Hz, 2H), 1.86 (d, *J*= 6.3 Hz, 3H); ^{13}C NMR δ 165.63 (C), 153.58 (C), 146.63 (CH), 141.14 (CH), 130.36 (CH), 117.53 (CH), 62.05 (CH_2), 42.77 (CH_2), 18.81 (CH_3); MS *m/z* 281 (M^+, 1), 119 ($C_4H_7O_2S$, 53), 83 (66), 79 (51), 69 (C_5H_9, 53), 55 (C_3H_3O, 100); HRMS calcd. for $C_9H_{11}NO_3Na$ 204.0631, found 204.0629; Anal. Calc. for $C_9H_{11}NO_3$: C, 58.93; H, 5.97; N, 7.71, Found: C, 58.78; H, 5.97; N, 7.63.

(*S*,*E*)-S-ethyl 5-methylnon-3-enethioate (**3.71b**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-S-ethyl nona-2,4-dienethioate and EtMgBr.
[0.5 mmol scale, 83% yield, 89% ee, >95:5 1,6:1,4, colorless oil]

$[\alpha]_D$= +9.0 (c= 1.0, $CHCl_3$); ^{1}H NMR δ 5.50-5.39 (m, 2H), 3.19 (d, *J*= 5.7 Hz, 2H), 2.84 (q, *J*= 7.4 Hz, 2H), 2.18-2.04 (m, 1H), 1.31-1.16 (m, 9H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.86 (t, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.7 (C), 142.6 (CH), 119.6 (CH), 47.9 (CH_2), 36.9 (CH), 36.7 (CH_2), 29.7 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 20.6 (CH_3), 14.9 (CH_3), 14.3 (CH_3); MS *m/z* 214 (M^+, 10), 124 (M-SEt-Et, 34), 83 (C_6H_{11}, 46), 69 (C_5H_9, 100); HRMS calcd. for $C_{12}H_{22}OS$ 214.1391, found 214.1401; Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 98°C in 4.8 min, 98 °C for 200 min; retention times (min): 163.8 (an enantiomer of the 1,4-addition product), 191.1 (*R*-enantiomer), 192.3 (*S*-enantiomer).

E-2-(4-ethyloct-2-enylsulfonyl)pyridine (**3.73a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2-(1*E*,3*E*-octa-1,3-dienylsulfonyl)pyridine and EtMgBr; upon addition of the substrate the solution turns bright red, upon quenching the solution becomes orange.
[0.25 mmol scale, 26% yield, 2% ee, 98:2 1,6:1,4, colorless oil]
^{1}H NMR δ 8.81-8.73 (m, 1H), 8.04 (dd, *J*= 7.8 Hz, 1.0 Hz, 1H), 7.92 (td, *J*= 7.7 Hz, 1.7 Hz, 1H), 7.52 (ddd, *J*= 7.7 Hz, 4.7 Hz, 1.2 Hz, 1H), 5.31 (dd, *J*= 5.1 Hz, 2.1 Hz, 2H), 4.11 (dd, *J*= 4.1 Hz, 2.0 Hz, 2H), 1.83-1.69 (m, 1H), 1.33-0.89 (m, 8H), 0.81 (t, *J*= 7.3 Hz, 3H), 0.63 (t, *J*= 7.4 Hz, 3H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 5.31 ppm and 4.11 ppm indicate 1,6-addition product; Enantiomeric excess and regioselectivity were determined by chiral HPLC analysis, column: chiralcel OD-H, (98:2 heptane:*i*PrOH); retention times (min): 33.0 (1,4-addition product), 34.3 (1,4-addition product), 37.2 (1,6-addition product), 39.4 (1,6-addition product).

E-1-(1-methyl-1H-imidazol-2-yl)-3-phenethylhex-4-en-1-one (**3.74c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using $BnCH_2MgBr$ and 2*E*,4*E*-1-(1-methyl-1H-imidazol-2-yl)hexa-2,4-dien-1-one.
[0.5 mmol scale, 98% conversion, 34% yield, 2% ee, 1,4:1,6 >95:5, colorless oil]
$[\alpha]_D$= +0.5 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.34-7.13 (m, 5H), 7.11 (s, 1H), 6.98 (s, 1H), 5.47 (dq, *J*= 15.2 Hz, 6.2 Hz, 1H), 5.34 (ddd, *J*= 15.2 Hz, 8.4 Hz, 1.4 Hz, 1H), 3.95 (s, 3H), 3.16 (ddd, *J*= 21.8 Hz, 15.8 Hz, 7.1 Hz, 2H), 2.77 (dt, *J*= 8.5 Hz, 5.5 Hz, 1H), 2.62 (dddd, *J*= 19.9 Hz, 13.8 Hz, 10.7 Hz, 5.7 Hz, 2H), 1.83-1.72 (m, 1H), 1.70-1.58 (m, 1H), 1.70-1.58 (m, 2H). Residual absorptions phenethyl alcohol: 7.34-7.13 (m, 5H), 3.85 (t, *J*= 6.7 Hz, 2H), 2.87 (t, *J*= 6.7 Hz, 2H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 3.85 ppm and 1.65 ppm and the coupling between the NMR signals at 3.16 and 2.77 ppm indicate 1,4-addition product; ^{13}C NMR δ 192.26 (C), 142.67 (C), 134.03 (CH), 129.08 (CH), 128.61 (CH), 128.45 (CH), 128.31 (CH), 126.89 (C), 125.82 (CH), 125.66 (CH), 44.67 (CH_2), 38.77 (CH_3), 37.11 (CH_2), 36.22 (CH), 33.63 (CH_2), 18.02 (CH_3). Residual absorptions phenethyl alcohol: 138.65 (C), 128.91 (CH), 128.31 (CH), 126.48 (CH), 63.68 (CH_2), 39.31 (CH_2); MS *m/z* 282 (M^+, 1), 254 (M^+-MeCH, 52), 191 (M^+-Bn, 61), 163 (M^+-MeCH-Bn, 69), 150 ($C_9H_{11}N_2O$, 58), 149 ($C_9H_{10}N_2O$, 62), 109 ($C_5H_5N_2O$, 93), 91 (Bn, 100), 83 (C_5H_7O, 60), 82 (C_5H_6O, 81); HRMS calcd. for $C_{18}H_{23}N_2O$ 283.1805, found 283.1805; Enantiomeric excess was determined by chiral HPLC analysis, column: chiralcel OJ-H, (95:5 heptane:*i*PrOH); retention times (min): 17.0 (minor), 18.4 (major). Ratio 1,6:1,4 was determined by ^{1}H NMR with d1=10.

E-3-(5-methylhept-3-enoyl)oxazolidin-2-one (**3.73b**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 3-2*E*,4*E*-hexa-2,4-dienoyloxazolidin-2-one and EtMgBr.
[0.25 mmol scale, 64% yield, 3% ee for 1,6-product, 75:25 1,6:1,4, colorless oil]
$[\alpha]_D^{20}$= +0.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.62-5.41 (m, 2H), 4.45-4.34 (m, 3H), 4.07-3.94 (m, 3H), 3.64 (d, *J*= 5.8 Hz, 2H), 2.04 (dt, *J*= 13.5 Hz, 6.8 Hz, 1H), 1.37-1.22 (m, 2H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.84 (t, *J*= 7.4 Hz, 3H). Residual absorptions 1,4-addition product: 5.40-5.20 (m, 2H), 4.45-4.34 (m, 3H), 4.07-3.94 (m, 3H), 3.70 (dt, *J*= 7.0 Hz, 1.7 Hz, 1H), 2.93 (qd, *J*= 15.7 Hz, 7.1 Hz, 2H), 2.50-2.41 (m, 1H), 1.63 (dd, *J*= 6.3 Hz, 1.5 Hz, 2H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 5.30 ppm and 3.64 ppm indicate 1,6-addition product; ^{13}C NMR δ 172.15 (C), 153.55 (C), 141.22 (CH), 119.37 (CH), 62.17 (CH_2), 42.66 (CH_2), 38.91 (CH_2), 38.47 (CH), 29.65 (CH_2), 20.06 (CH_3), 11.79 (CH_3); MS *m/z* 211 (M^+, 8), 182 (M^+-Et, 35), 96 (C_6H_8O, 36), 95 (C_6H_7O, 100), 55 (C_3H_3O, 24);

HRMS calcd. for $C_{11}H_{17}NO_3Na$ 234.1101, found 234.1097; regioselectivity was determined by 1H NMR with d1= 10 s; Ee was determined by chiral GC analysis for 2-methylbutanoic acid,[31,xvii] column: Chiraldex-B-PM, 50 °C to 60 °C in 1 min, 60 °C for 70 min, 60 °C to 160 °C in 10 min, 160 °C for 4 min; retention times (min): 81.6 (major), 82.0 (minor).

Influence of substitution pattern for 1,6-ACA:
General procedure for the synthesis of α-Me-substituted α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction:[20]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, triethyl phosphonopropionate (1.2 equiv) was dissolved in anhydrous THF (4 mL/mmol aldehyde) and cooled to −78 °C. *n*BuLi (1.6 M solution in hexanes, 1.15 equiv) was added dropwise and the mixture was stirred for 30 min. Subsequently, the aldehyde (1 equiv) dissolved in anhydrous THF (1 mL/mmol aldehyde) was added dropwise. After addition, the solution was allowed to warm up to rt and stirred for 16 h. The reaction mixture was diluted with Et_2O (5 mL/mmol aldehyde) and the solution was subsequently washed with NH_4Cl (saturated aq solution, 5 mL/mmol aldehyde), Na_2CO_3 (saturated aq solution, 5 mL/mmol aldehyde) and brine (5 mL/mmol aldehyde). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2*E*,4*E*-ethyl 2-methylnona-2,4-dienoate (**3.49a**) was prepared via the general procedure for the synthesis of α-Me-substituted α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction using *E*-hept-2-enal.
[10 mmol scale, 90% yield, *E*:*Z* 16:1, colorless oil]
^{1}H NMR δ 7.13 (d, *J*= 11.3 Hz, 1H), 6.37-6.24 (m, 1H), 6.12-5.97 (m, 1H), 4.16 (q, *J*= 7.1 Hz, 2H), 2.15 (q, *J*= 7.0 Hz, 2H), 1.89 (d, *J*= 0.8 Hz, 3H), 1.46-1.20 (m, 7H), 0.87 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR δ 168.62 (C), 143.10 (CH), 138.59 (CH), 126.02 (CH), 125.06 (C), 60.41 (CH_2), 33.02 (CH_2), 31.15 (CH_2), 22.30 (CH_2), 14.36 (CH_3), 13.91 (CH_3), 12.55 (CH_3); *m/z* 196 (M^+,47), 151 (M^+-OEt, 30), 139 ($C_8H_{10}O_2$, 100), 112 (35), 111 ($C_6H_7O_2$, 85); HRMS calcd. for $C_{12}H_{20}O_2Na$ 219.1356, found 219.1355.

2*E*,4*E*-ethyl 3-methylnona-2,4-dienoate (**3.49i**) was prepared via the procedure described in ref 21.
[4.9 mmol scale, 8% yield, colorless oil]
Data were in accordance to those given in ref 21; additional data: *m/z* 196 (M^+,10), 139 ($C_8H_{10}O_2$, 96), 111 ($C_6H_7O_2$, 100); HRMS calcd. for $C_{12}H_{21}O_2$ 197.1536, found 197.1536.

General procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction:[16]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, NaH (1.75 equiv) was vigorously stirred in anhydrous THF (1 mL/mmol aldehyde) and cooled to −20 °C. Triethyl phosphonoacetate (neat, 1.75 equiv) was added dropwise and the mixture was stirred for 30 min. Subsequently, the aldehyde (1 equiv) dissolved in anhydrous THF (0.1 mL/mmol aldehyde) was added dropwise. After addition, the solution was stirred for 20 min at −20 °C and subsequently stirred at rt for 30 min. The reaction mixture was diluted with Et_2O (2 mL/mmol aldehyde) and the solution was subsequently washed with NH_4Cl (saturated aq solution, 2 mL/mmol aldehyde), Na_2CO_3 (saturated aq solution, 2 mL/mmol aldehyde) and brine (2 mL/mmol aldehyde). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2*E*,4*E*-ethyl 4-methylhexa-2,4-dienoate (**3.49b**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction using *E*-2-methylbut-2-enal.
[10 mmol scale, 89% yield, *Z*-isomer not observed, colorless oil]

Data were in accordance to those given in ref 34; additional data: ^{13}C NMR δ 167.75 (C), 149.59 (CH), 136.41 (CH), 133.87 (C), 115.37 (CH), 60.23 (CH_2), 14.65 (CH_3), 14.45 (CH_3), 11.88 (CH_3); MS *m/z* 154 (M^+, 69), 139 (M^+-CH_3, 47), 111 ($C_6H_7O_2$, 86), 109 (M^+-OEt, 54), 83 ($C_4H_3O_2$, 58), 81 (M^+-CO_2Et, 100); HRMS calcd. for $C_9H_{14}O_2$ 154.0994, found 154.0987.

E-ethyl 5-methylhexa-2,4-dienoate (**3.49c**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction using 3-methylbut-2-enal.
[10 mmol scale, 84% yield, *Z*-isomer not observed, colorless oil]
Data were in accordance to those given in ref 35; additional data: ^{13}C NMR δ 167.51 (C), 145.96 (C), 140.82 (CH), 123.71 (CH), 118.58 (CH), 59.96 (CH_2), 26.42 (CH_3), 18.81 (CH_3), 14.27 (CH_3); HRMS calcd. for $C_9H_{14}O_2Na$ 177.0886, found 177.0884.

(5*R*,*E*)-ethyl 5-ethyl-2-methylnon-3-enoate (**3.77a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-ethyl 2-methylnona-2,4-dienoate and EtMgBr.
[0.5 mmol scale, 94% conversion, 83% yield, 1:1 mixture of *cis* and *trans* diastereomers, 97% ee,1,6:1,4 >99:1, colorless oil]
$[\alpha]_D^{20}$= +2.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.42 (dd, *J*= 15.3 Hz, 7.8 Hz, 1H), 5.23 (dd, *J*= 15.3 Hz, 8.8 Hz, 1H), 4.23-3.99 (m, 2H), 3.22-2.89 (m, 1H), 1.88-1.72 (m, 1H), 1.53-1.02 (m, 13H), 0.99-0.64 (m, 6H); ^{13}C NMR δ 175.28 (C), 136.64 (CH), 129.04 (CH), 60.46 (CH_2), 44.53 (CH), 43.11 (CH), 34.77 (first diastereomer CH_2), 34.74 (second diastereomer CH_2), 29.58 (CH_2), 28.10 (CH_2), 22.90 (CH_2), 17.69 (CH_3), 14.33 (CH_3), 14.23 (CH_3), 11.80 (CH_3); MS first diastereomer *m/z* 226 (M^+, 10), 102 ($C_5H_{10}O_2$, 100), 95 (C_6H_7O, 44), 69 (C_5H_9, 47), 55 (C_3H_3O, 69), second diastereomer *m/z* 226 (M^+, 10), 102 ($C_5H_{10}O_2$, 100), 95 (C_6H_7O, 45), 69 (C_5H_9, 47), 55 (C_3H_3O, 70); HRMS calcd. for $C_{14}H_{26}O_2Na$ 249.1825, found 249.1822; Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 110 °C in 6 min, 110 °C for 90 min; retention times (min): 38.4 (an enantiomer of the 1,4-addition product), 51.3 (major enantiomer of the first diastereomer), 52.0 (minor enantiomer of the first diastereomer), 52.9 (minor enantiomer of the second diastereomer), 54.1 (major enantiomer of the second diastereomer).

A mixture of 27% *Z*-ethyl 4,5-dimethylhept-3-enoate and 73% *E*-ethyl 4,5-dimethylhept-3-enoate (**3.77c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-ethyl 4-methylnona-2,4-dienoate and EtMgBr; reaction time 40 h, reaction temperature −60 °C.
[0.5 mmol scale, 94% conversion, 83% yield, 0% ee, > 92% 1,6-addition product, colorless oil]
$[\alpha]_D^{20}$= +1.3 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.38-5.28 (m, 1H), 4.12 (qd, *J*= 7.1 Hz, 1.6 Hz, 2H), 3.09-2.98 (m, 2H), 2.45 (*E*-product, dt, *J*= 13.9 Hz, 7.0 Hz, 1H), 2.03 (*Z*-product, dd, *J*= 14.1 Hz, 7.0 Hz, 1H), 1.60 (*E*-product, d, *J*= 1.3 Hz, 3H), 1.52 (*Z*-product, s, 5H), 1.49 (1,4-addition product, s, 1H), 1.38-1.27 (m, 2H), 1.24 (t, *J*= 7.1 Hz, 3H), 0.96 (*E*-product, t, *J*= 7.3 Hz, 3H), 0.87 (*Z*-product, t, *J*= 7.0 Hz, 3H), 0.79 (td, *J*= 7.4, 1.6 Hz, 3H); GCOSY ^{1}H NMR: Coupling of the overlapping NMR signals for both the E- and Z-product at 5.38-5.28 ppm and 3.09-2.984 ppm indicate *Z*- and *E*- 1,6-addition product;^{13}C NMR δ 172.64 (C), 143.04 (C), 116.39 (*E*-product, CH), 115.42 (*Z*-product, CH), 60.56 (*E*-product, CH_2), 60.52 (*Z*-product, CH_2), 44.53 (*Z*-product, CH), 36.21 (*E*-product, CH), 33.80 (*Z*-product, CH_2), 33.33 (*E*-product, CH_2), 27.77 (*Z*-product, CH_2), 27.64 (*E*-product, CH_2), 19.33 (*Z*-product, CH_3), 18.92 (*E*-product, CH_3), 18.04 (*Z*-product, CH_3), 14.34 (*E*-product, CH_3), 12.30 (*E*-product, CH_3), 12.13 (*Z*-product, CH_3); MS *m/z* 184 (M^+, 27), 110 ($C_7H_{10}O$, 40), 97 ($C_5H_5O_2$, 43), 96 (C_6H_8O, 68), 81 (C_5H_5O, 47), 69 (C_5H_9, 93), 55 (C_3H_3O, 100); HRMS calcd. for $C_{11}H_{21}O_2$ 185.1536, found 185.1535; Ratio *E*- and *Z*-product was determined by ^{1}H NMR with d1= 10 s; Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 110 °C in 6 min, 110 °C for 90 min; retention times (min): 84.2 (an enantiomer of *E*-product), 95.1 (an enantiomer of *E*-product), 100.1 (an enantiomer of *Z*-product), 102.4 (an enantiomer of *Z*-product).

Influence of olefin geometry:
2*E*,4*E*-ethyl deca-2,4-dienoate (**3.49d**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction using *E*-oct-2-enal.
[4.0 mmol scale, 93% yield, colorless oil]
Data were in accordance to those given in ref 36; additional data: MS *m/z* 196 (M^+, 37), 151 (M^+-OEt, 34), 125 ($C_7H_9O_2$, 100), 98 (35), 97 ($C_5H_5O_2$, 79), 81 (C_5H_5O, 72), 67 (C_4H_3O, 59); HRMS (APCI+) calcd. for $C_{12}H_{21}O_2$ 197.1536, found 197.1529.

E-ethyl dec-2-en-4-ynoate (**3.49e**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction using oct-2-ynal.
[6.0 mmol scale, 84% yield, colorless oil]
^{1}H NMR δ 6.71 (ddd, *J*= 15.8 Hz, 3.1 Hz, 1.4 Hz, 1H), 6.09 (dd, *J*= 15.8, 0.6 Hz, 1H), 4.16 (qd, *J*= 7.1 Hz, 1.6 Hz, 2H), 2.32 (td, *J*= 7.1 Hz, 1.7 Hz, 2H), 1.60-1.43 (m, 2H), 1.42-1.11 (m, 7H), 0.86 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 166.12 (C), 129.28 (CH), 126.13 (CH), 100.80 (C), 77.99 (C), 60.56 (CH_2), 31.09 (CH_2), 28.08 (CH_2), 22.22 (CH_2), 19.76 (CH_2), 14.24 (CH_3), 13.96 (CH_3); MS *m/z* 194 (M^+, 1), 149 (M^+-OEt, 57), 119 (C_8H_7O, 65), 109 ($C_6H_5O_2$, 64), 93 ($C_6H_5O_2$, 70), 91 (76), 79 (C_5H_3O, 100), 55 (C_3H_3O, 63); HRMS calcd. for $C_{12}H_{19}O_2$ 195.1380, found 195.1371.

General procedure for the reduction of alkynes to *Z*-alkenes:[22]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, Lindlar catalyst (50 mg/mmol substrate, 5 wt % Pd on $CaCO_3$, poisoned with led, ~2.3 mol% Pd) was stirred in anhydrous CH_2Cl_2 (15 mL/mmol substrate). Quinoline (8 mol%) was added, followed by the substrate (1.0 equiv), and the system was put under a H_2 atmosphere by three H_2/vacuum cycles. The reaction mixture was stirred for 50 min and subsequently filtered over celite. After evaporation of the solvent, flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2*E*,4*Z*-ethyl deca-2,4-dienoate (**3.49j**) was prepared via the general procedure for the reduction of alkynes to *Z*-alkenes using *E*-ethyl dec-2-en-4-ynoate.
[2.2 mmol scale, 43% yield, colorless oil]
Data were in accordance to those given in ref 37; additional data: MS *m/z* 196 (M^+, 37), 151 (M^+-OEt, 34), 125 ($C_7H_9O_2$, 100), 98 (35), 97 ($C_5H_5O_2$, 79), 81 (C_5H_5O, 72), 67 (C_4H_3O, 59); HRMS (APCI+) calcd. for $C_{12}H_{21}O_2$ 197.1536, found 197.1528.

General procedure for the synthesis of 2*Z*-α,β,γ,δ-bisunsaturated alkenes via HWE reaction:[23]
A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_2CH_3$ (1.0 equiv) and 18-crown-6 (3.0 equiv) in THF (6.6 mL/mmol substrate) was cooled to −78 °C and treated with *t*-BuOK (1.0 equiv). After the mixture was stirred for 15 min, a solution of the aldehyde (1.0 equiv) in THF (1.1 mL/mmol substrate) was added by syringe pump with 30 min addition time. The resulting mixture was stirred at −78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and the bulk of THF was removed under reduced pressure. The residue was extracted with Et_2O (3 x 3 ml/mmol substrate) and the organic extracts were washed with brine, dried and concentrated. A solution of the crude product in pentane was decanted away from the residual 18-crown-6 and was purified by flash column chromatography (gradient pentane to 2:98 Et_2O:pentane).

2*Z*,4*E*-ethyl deca-2,4-dienoate (**3.49g**) was prepared via the general procedure for the synthesis of *Z*-α,β-unsaturated alkenes via HWE reaction using *E*-oct-2-enal.
[3.0 mmol scale, 56 % yield (pure 2*Z*,4*E*-compound, incomplete reaction), colorless oil]

^{1}H NMR δ 7.40-7.30 (m, 1H), 6.52 (t, *J*= 11.4 Hz, 1H), 6.09-5.99 (m, 1H), 5.53 (d, *J*= 11.3 Hz, 1H), 4.15 (q, *J*= 7.1 Hz, 2H), 2.17 (q, *J*= 7.4 Hz, 2H), 1.48-1.37 (m, 2H), 1.33-1.22 (m, 7H), 0.86 (t, *J*= 7.0 Hz, 3H); ^{13}C NMR δ 166.63 (C), 145.79 (CH), 145.45 (CH), 127.00 (CH), 115.55 (CH), 59.86 (CH_2), 33.05 (CH_2), 31.53 (CH_2), 28.55 (CH_2), 22.57 (CH_2), 14.38 (CH_3), 14.07 (CH_3); MS *m/z* 196 (M^+, 21), 125 ($C_7H_9O_2$, 100), 97 ($C_5H_5O_2$, 76), 81 (C_5H_5O, 37), 67 (C_4H_3O, 33); HRMS calcd. for $C_{12}H_{21}O_2$ 197.1536, found 197.1532.

Z-oct-2-enal (**3.52h**) was prepared via the general procedure for the reduction of alkynes to *Z*-alkenes using octynal, reaction time 16 h (presumably the Lindlar catalyst was deactivated by storage and with a fresh badge of Lindlar catalyst reaction time can be reduced).
[10 mmol scale, 51% yield *Z*-product, *Z*:*E* ~6:1 colorless oil]
Data were in accordance to those given in ref 38.

2*Z*,4*Z*-ethyl deca-2,4-dienoate (**3.49h**) was prepared via the general procedure for the synthesis of *Z*-α,β-unsaturated alkenes via HWE reaction using *Z*-oct-2-enal.
[3.0 mmol scale, 70% yield of a mixture of 45.7%:35.6%:17.9%:0.9% 2*Z*,4*Z*:2*Z*,4*E*:2*E*,4*Z*:2*E*,4*E* product, colorless oil]
^{1}H NMR δ 7.30-7.21 (m, 1H), 6.91 (td, *J*= 11.8, 1.0 Hz, 1H), 5.94-5.84 (m, 1H), 5.65 (d, *J*= 11.5 Hz, 1H), 4.14 (q, *J*= 7.1 Hz, 2H), 2.24 (q, *J*= 7.7 Hz, 2H), 1.48-1.35 (m, 2H), 1.35-1.21 (m, 7H), 0.87 (t, *J*= 6.9 Hz, 3H); ^{13}C NMR δ 166.69 (C), 141.74 (CH), 138.99 (CH), 124.53 (CH), 117.45 (CH), 60.00 (CH_2), 34.24 (CH_2), 31.56 (CH_2), 29.16 (CH_2), 27.57 (CH_2), 14.41 (CH_3), 14.10 (CH_3); MS *m/z* 196 (M^+, 20), 125 ($C_7H_9O_2$, 100), 97 ($C_5H_5O_2$, 77), 81 (C_5H_5O, 41), 67 (C_4H_3O, 36); HRMS calcd. for $C_{12}H_{21}O_2$ 197.1536, found 197.1532.

(*R*,*E*)-ethyl 5-ethyldec-3-enoate (**3.79**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2*E*,4*E*-ethyl deca-2,4-dienoate and EtMgBr or 2*E*,4*Z*-ethyl deca-2,4-dienoate [a mixture of 1.0:0.1 2*E*,4*Z*:2*E*,4saturated substrate] and EtMgBr or 2*Z*,4*E*-ethyl deca-2,4-dienoate and EtMgBr or 2*Z*,4*Z*)-ethyl deca-2,4-dienoate [a mixture of 1.2:1.0:0.8 2*Z*,4*E*:2*Z*,4*Z*:2*E*,4*E* substrate] and EtMgBr.
[from 2*E*,4*E*-substrate, 0.5 mmol scale, 80% yield, 93% ee (*R*-enantiomer), 1,6:1,4 98:2, colorless oil]
[from 2*E*,4*Z*-substrate with (*S*,*R*)-catalyst, 0.5 mmol scale, 73% yield, 91% ee (*R*-enantiomer), 1,6:1,4 98:2, colorless oil]
[from 2*Z*,4*E*-substrate, 0.5 mmol scale, 71% yield, 3% ee (*S*-enantiomer), 1,6:1,4 99:1, colorless oil]
[from 2*Z*,4*Z*-substrate, 0.5 mmol scale, 72% yield, 30% ee (*R*-enantiomer), 1,6:1,4 99:1, colorless oil]
$[\alpha]_D^{20}$= −0.9 (c=1.0, CH_2Cl_2, for 93% ee); ^{1}H NMR δ 5.52-5.41 (m, 1H), 5.25 (ddt, *J*= 15.3 Hz, 8.8 Hz, 1.2 Hz, 1H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.01 (dd, *J*= 6.9 Hz, 1.2 Hz, 2H), 1.84 (dt, *J*= 8.3 Hz, 4.4 Hz, 1H), 1.47-1.11 (m, 13H), 0.92-0.76 (m, 6H); ^{13}C NMR δ 172.32 (C), 139.18 (CH), 121.62 (CH), 60.55 (CH_2), 44.61 (CH), 38.41 (CH_2), 34.93 (CH_2), 32.13 (CH_2), 28.01 (CH_2), 27.00 (CH_2), 22.78 (CH_2), 14.32 (CH_3), 14.22 (CH_3), 11.78 (CH_3); MS *m/z* 226 (M^+, 8), 124 ($C_8H_{12}O$, 100), 109 (C_7H_9O, 99), 81 (C_5H_5O, 86), 67 (C_4H_3O, 74), 55 (C_3H_3O, 76); HRMS calcd. for $C_{14}H_{26}O_2Na$ 249.1825, found 249.1820; Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 110 °C in 6 min, 110 °C for 90 min; retention times (min): 84.5 (an enantiomer of the 1,4-addition product), 85.5 (other enantiomer of the 1,4-addition product), 92.0 (*S*-enantiomer), 93.0 (*R*-enantiomer).

1,8- and 1,10-addition:
2*E*,4*E*,6*E*-ethyl undeca-2,4,6-trienoate (**3.49f**) was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner- Wadsworth-Emmons reaction using 2*E*,4*E*-nona-2,4-dienal.
[10.0 mmol scale, 75% yield, 6:1 all-*E*:mono *Z*, slightly yellow oil]

^{1}H NMR δ 7.27 (dd, *J*= 14.8 Hz, 11.3 Hz, 1H), 6.50 (dd, *J*= 14.8 Hz, 10.7 Hz, 1H), 6.14 (ddd, *J*= 29.4 Hz, 14.6 Hz, 11.0 Hz, 2H), 5.96-5.85 (m, 1H), 5.81 (d, *J*= 15.3 Hz, 1H), 4.17 (qd, *J*= 7.1 Hz, 1.3 Hz, 2H), 2.12 (q, *J*= 7.0 Hz, 2H), 1.44-1.22 (m, 7H), 0.88 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 167.23 (C), 144.85 (CH), 141.23 (CH), 140.62 (CH), 129.90 (CH), 127.82 (CH), 120.09 (CH), 60.21 (CH_2), 32.73 (CH_2), 31.19 (CH_2), 22.32 (CH_2), 14.39 (CH_3), 13.95(CH_3); MS *m/z* 208 (M^+, 43), 119 ($C_8H_7O_2$, 36), 91 (C_7H_7, 76), 79 (C_5H_3O, 100), 77 (42), 57 (C_4H_9, 42); HRMS (APCI+) calcd. for $C_{13}H_{21}O_2$ 209.1536, found 209.1528.

Synthesis of S-ethyl 2-(diethoxyphosphoryl)ethanethioate (**3.60**):
In a dried roundbottom two necked flask equipped with septum and stirring bar under a N_2 atmosphere, 2-(diethoxyphosphoryl)acetic acid (1.0 equiv) and DMAP (0.1 equiv) were dissolved in anhydrous CH_2Cl_2 (1.5 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and subsequently EtSH (1.05 equiv) and DCC (1.05 equiv) in CH_2Cl_2 (0.5 mL/mmol substrate) were added. After stirring for 4 h (0 °C to rt) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract were dried and concentrated to a yellow oil. Flash column chromatography (gradient 20% EtOAc/pentane to 100% EtOAc/automated column) yielded the product in ~60% as a colorless oil (with traces of $OPPh_3$).

General procedure for the synthesis of α,β,γ,δ,ε,ζ-triple unsaturated thioesters from α,β,γ,δ-bisunsaturated aldehydes via Horner- Wadsworth-Emmons reaction.
In a round bottom flask equipped with stirring bar S-ethyl 2-(diethoxyphosphoryl)ethanethioate (1.5 equiv) is dissolved in anhydrous THF (20.0 mL/mmol substrate) and cooled to 0 °C. *n*BuLi (1.6 M in Et_2O, 1.4 equiv) is added drop wise and the reaction mixture is stirred for 30 min and then cooled to −78 °C. Then, the aldehyde substrate (1 equiv) dissolved in anhydrous THF (2.0 mL/mmol substrate) was added dropwise. After addition, the solution was allowed to warm to rt and stirred in total for 16 h. Then an aq solution of NH_4Cl (1 M, 1 mL) was added and the mixture extracted with Et_2O (3x 2 mL). The combined organic extracts were dried and concentrated. Flash column chromatography (1:99 Et_2O:pentane) yielded the product.

2*E*,4*E*,6*E*-S-ethyl undeca-2,4,6-trienethioate (**3.61**) was prepared via the general procedure for the synthesis of α,β,γ,δ,ε,ζ-triple unsaturated thioesters from α,β,γ,δ-bisunsaturated aldehydes via Horner-Wadsworth-Emmons reaction using 2*E*,4*E*-nona-2,4-dienal.
[6.0 mmol scale, 61% yield, 9:1 all-*E*:mono *Z,* yellow oil]
^{1}H NMR δ 7.19 (dd, *J*= 15.1 Hz, 11.4 Hz, 2H), 6.55 (dd, *J*= 14.8 Hz, 10.7 Hz, 2H), 6.22-5.98 (m, 6H), 5.98-5.82 (m, 2H), 2.92 (qd, *J*= 7.4 Hz, 1.2 Hz, 4H), 2.11 (q, *J*= 7.1 Hz, 4H), 1.43-1.12 (m, 15H), 0.87 (t, *J*= 7.2 Hz, 7H); ^{13}C NMR δ 189.61 (C), 142.64 (CH), 141.13 (CH), 140.62 (CH), 129.97 (CH), 127.62 (CH), 127.09 (CH), 32.75 (CH_2), 31.10 (CH_2), 23.19 (CH_2), 22.29 (CH_2), 14.91 (CH_3), 13.93 (CH_3); MS *m/z* 224 (M^+, 11), 163 (M^+-SEt, 80), 107 (C_7H_6O, 100), 91 (C_7H_7. 31), 91 (C_5H_9. 45); HRMS calcd. for $C_{13}H_{20}OSNa$ 247.1127, found 247.1124.

Synthesis of 2*E*,4*E*,6*E*,8*E*-ethyl trideca-2,4,6,8-tetraenoate (**3.49k**) from 2*E*,4*E*,6*E*-ethyl undeca-2,4,6-trienoate:
1) General procedure for the reduction of an unsaturated ester to the allylic alcohol:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere the ester was dissolved in anhydrous CH_2Cl_2 (5 mL). After 5 min stirring at rt the mixture was cooled to −70 °C and DIBAL-H (1.0 M solution in CH_2Cl_2, 2.1 equiv) was added. The reaction mixture was stirred for 16 h at −70 °C. Subsequently the reaction mixture was poured into a roundbottom flask with aq Rochelle's salt-solution (saturated, 10 mL), stirred for 1 h at rt and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were washed with the aq Rochelle's salt-solution (2x 5 mL), dried and carefully concentrated. The alcohol was used without further purification in the subsequent IBX oxidation.
2) IBX oxidation of the allylic alcohol was performed according to ref 39. The aldehyde was used without further purification for the HWE reaction.

3) The product was prepared via the general procedure for the synthesis of α,β,γ,δ-bisunsaturated esters from α,β-unsaturated aldehydes via Horner-Wadsworth-Emmons reaction.

[6.0 mmol scale, 20% yield (3 steps), 7:1 all-*E*:mono *Z,* white solid]
^{1}H NMR δ 7.29 (dd, *J*= 15.2 Hz, 11.4 Hz, 1H), 6.54 (dd, *J*= 14.7 Hz, 11.0 Hz, 1H), 6.40-6.04 (m, 4H), 5.88-5.76 (m, 2H), 4.18 (q, *J*= 7.1 Hz, 2H), 2.11 (q, *J*= 7.0 Hz, 2H), 1.44-1.21 (m, 7H), 0.88 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 167.19 (C), 144.62 (CH), 141.07 (CH), 138.77 (CH), 137.71 (CH), 130.28 (CH), 129.62 (CH), 129.14 (CH), 120.17 (CH), 60.22 (CH_2), 32.73 (CH_2), 31.33 (CH_2), 22.31 (CH_2), 14.39 (CH_3), 13.96 (CH_3); MS *m/z* 234 (M^+, 38), 131 ($C_{10}H_{11}$, 31), 117 (C_9H_9, 73), 105 (C_8H_9, 55), 91 (C_7H_7. 100), 79 (C_6H_7, 32); HRMS calcd. for $C_{15}H_{23}O_2$ 235.1693, found 235.1694.

Synthesis of 2*E*,4*E*,6*E*,8*E*-S-ethyl trideca-2,4,6,8-tetraenethioate (**3.63**) from 2*E*,4*E*,6*E*-ethyl undeca-2,4,6-trienoate:
Step 1) and 2) are according to the synthesis of 2*E*,4*E*,6*E*,8*E*-ethyl trideca-2,4,6,8-tetraenoate from 2*E*,4*E*,6*E*-ethyl undeca-2,4,6-trienoate.
3) The product was prepared via the general procedure for the synthesis of α,β,γ,δ,ε,ζ-triple unsaturated thioesters from α,β,γ,δ-bisunsaturated aldehydes via Horner- Wadsworth-Emmons reaction.
[6.0 mmol scale, 23% yield (3 steps), 8:1 all-*E*:mono *Z,* yellow solid]
^{1}H NMR δ 7.32-7.13 (m, 1H), 6.61 (dd, *J*= 14.5 Hz, 11.2 Hz, 1H), 6.37 (dd, *J*= 14.8 Hz, 10.7 Hz, 1H), 6.31-6.00 (m, 4H), 5.90-5.79 (m, 1H), 2.94 (qd, *J*= 7.4 Hz, 1.2 Hz, 2H), 2.12 (q, *J*= 7.0 Hz, 2H), 1.45-1.13 (m, 7H), 0.88 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 189.63 (C), 142.55 (CH), 140.44 (CH), 139.25 (CH), 138.17 (CH), 130.29 (CH), 129.70 (CH), 129.00 (CH), 127.15 (CH), 32.78 (CH_2), 31.29 (CH_2), 23.27 (CH_2), 22.33 (CH_2), 14.95 (CH_3), 13.99 (CH_3); MS *m/z* 250 (M^+, 22), 189 (M^+-SEt, 55), 133 (C_9H_9O, 100), 107 (C_7H_6O, 66), 91 (C_7H_7. 78); HRMS calcd. for $C_{15}H_{23}OS$ 251.1464, found 251.1457.

(*R*,*3E*,*5E*)-ethyl 7-ethylundeca-3,5-dienoate (**3.81f**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition.
[0.5 mmol scale, 47% yield (combined yield 1,8-, 1,6- and 1,4-addition products), 7% ee, 1,8:1,6:1,4 63:8:29, colorless oil]
$[\alpha]_D^{20}$= +1.5 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 6.10 (dd, *J*= 15.1 Hz, 10.3 Hz, 1H), 6.02-5.94 (m, 1H), 5.63 (dt, *J*= 22.5 Hz, 7.3 Hz, 1H), 5.38 (dd, *J*= 14.8 Hz, 8.9 Hz, 1H), 4.20-4.05 (m, 3H), 3.08 (dd, *J*= 7.2 Hz, 1.0 Hz, 2H), 1.92-1.80 (m, 1H), 1.48-1.12 (m, 11H), 0.91-0.78 (m, 6H). Residual absorptions side-products: 3.24-3.19 (1,6-addition product, m, 2H), 2.43 (1,6-addition product, dd, *J*= 8.3 Hz, 5.4 Hz, 1H), 2.30 (1,4-addition product, ddd, *J*= 22.7 Hz, 14.5 Hz, 7.2 Hz, 2H), 2.04 (1,4-addition product, q, *J*= 7.0 Hz, 1H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 2.25 ppm and 2.05 ppm and the coupling between the NMR signals at 5.58 and 2.05 ppm indicate 1,4-addition product, Coupling between the NMR signals at 5.63 ppm and 3.08 ppm and the coupling between the NMR signals at 5.39 and 1.85 ppm indicate 1,8-addition product; ^{13}C NMR δ 172.77 (1,4-addition, C), 171.97 (1,8-addition, C), 139.45 (1,8-addition, CH), 134.23 (1,8-addition, CH), 133.81 (1,4-addition, CH), 133.57 (1,4-addition, CH), 131.24 (1,4-addition, CH), 130.15 (1,4-addition, CH), 129.51 (1,8-addition, CH), 122.43 (1,8-addition, CH), 60.77 (1,8-addition, CH_2), 60.27 (1,4-addition, CH_2), 44.73 (1,8-addition, CH), 41.21 (1,4-addition, CH), 40.33 (1,4-addition, CH_2), 38.27 (1,8-addition, CH_2), 34.83 (1,8-addition, CH_2), 32.41 (1,4-addition, CH_2), 31.62 (1,4-addition, CH_2), 29.69 (1,8-addition, CH_2), 28.18 (1,8-addition, CH_2), 27.89 (1,4-addition, CH_2), 22.98 (1,8-addition, CH_2), 22.38 (1,4-addition, CH_2), 14.42 (1,4-addition, CH_3), 14.34 (1,8-addition, CH_3), 14.21 (1,8-addition, CH_3), 14.06 (1,4-addition, CH_3), 11.89 (1,8-addition, CH_3), 11.69 (1,4-addition, CH_3); MS *m/z* 238 (M^+, 25), 135 ($C_9H_{11}O$, 68), 121 (C_8H_9O, 48), 107 (C_7H_7O, 100), 93 (C_7H_9, 85), 79 (C_6H_7. 91), 67 (C_4H_3O, 64); HRMS calcd. for $C_{15}H_{26}O_2Na$ 261.1825, found 261.1820; Ee was determined by chiral GC analysis for 2-ethylhexanoic acid,[xvii] column: Chiraldex-B-PM, 50 °C to 120 °C in 7 min, 120 °C for 70 min; retention times (min): 41.2 (major), 43.2 (minor). Regioselectivity was determined by ^{1}H NMR with d1=10 s.

(*R*,3*E*,5*E*)-S-ethyl 7-methylundeca-3,5-dienethioate (**3.81l**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition, 48 h reaction time, 7.5% catalyst.
[0.5 mmol scale, 91% conversion, 63% yield (combined yield 1,8- and 1,4- product), 72% ee, 1,8:1,4 86:14, colorless oil]
$[\alpha]_D^{20}$= −13.4 (c=0.5, CH_2Cl_2); ^{1}H NMR δ 6.13 (dd, *J*= 15.0, 10.4 Hz, 1H), 5.99 (dd, *J*= 15.2 Hz, 10.3 Hz, 1H), 5.69-5.52 (m, 2H), 3.28 (dd, *J*= 7.3, 0.9 Hz, 2H), 2.87 (q, *J*= 7.4 Hz, 2H), 2.19-2.08 (m, 1H), 1.36-1.18 (m, 9H), 0.98 (d, *J*= 6.7 Hz, 3H), 0.91-0.84 (m, 3H); Residual absorptions 1,4-product: 2.80-2.71 (m, 1H), 2.52 (ddd, *J*= 22.1 Hz, 14.5 Hz, 7.2 Hz, 2H), 2.08-2.01 (m, 1H), 1.05 (d, *J*= 6.7 Hz, 3H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 2.75 ppm and 2.53 ppm and the coupling between the NMR signals at 5.48 and 2.75 ppm indicate 1,4-addition product, coupling between the NMR signals at 5.60 ppm and 3.27 ppm and the coupling between the NMR signals at 5.56 and 2.12 ppm indicate 1,8-addition product; ^{13}C NMR δ 198.00 (C), 141.60 (1,8-addition, CH), 135.54 (1,8-addition, CH), 135.13 (1,4-addition, CH), 133.94 (1,4-addition, CH), 130.07 (1,4-addition, CH), 129.65 (1,4-addition, CH), 127.68 (1,8-addition, CH), 122.01 (1,8-addition, CH), 51.13 (1,4-addition, CH_2), 47.72 (1,8-addition, CH_2), 36.88 (1,8-addition, CH), 36.80 (1,8-addition, CH_2), 34.28 (1,4-addition, CH), 32.43 (1,4-addition, CH_2), 31.63 (1,4-addition, CH_2), 29.69 (1,8-addition, CH_2), 23.54 (1,8-addition, CH_2), 23.46 (1,4-addition, CH_2), 22.95 (1,8-addition, CH_2), 22.38 (1,4-addition, CH_2), 20.55 (1,8-addition, CH_3), 20.01 (1,4-addition, CH_3), 14.94 (1,4-addition, CH_3), 14.81 (1,8-addition, CH_3), 14.22 (1,8-addition, CH_3), 14.07 (1,4-addition, CH_3); MS *m/z* 240 (M^+, 11), 95 (C_6H_7O, 64), 81 (C_5H_5O, 69), 79 (C_6H_7. 39), 67 (C_4H_3O, 100); HRMS calcd. for $C_{14}H_{25}OS$ 241.1621, found 214.1621; Ee was determined by chiral GC analysis for 2-methylhexanoic acid,[xvii] column: Chiraldex-B-PM, 50 °C to 130 °C in 8 min, 130 °C for 70 min; retention times (min): 22.6 (minor), 23.8 (major). Regioselectivity was determined by ^{1}H NMR with d1= 10 s.

(*R*,3*E*,5*E*,7*E*)-ethyl 9-ethyltrideca-3,5,7-trienoate (**3.81k**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition, 48 h reaction time.
[0.5 mmol scale, 85% conversion, 22% yield (combined yield 1,10-, 1,8-/1,6- and 1,4-addition products), 1,8-product 12% ee, 1,10:1,8/1,6:1,4 49:8:43, colorless oil]
$[\alpha]_D^{20}$= +1.4 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 6.24-5.94 (m, 4H), 5.69 (qd, *J*= 14.0 Hz, 6.7 Hz, 1H), 5.44 (dd, *J*= 15.0 Hz, 9.0 Hz, 1H), 4.20-4.05 (m, 2H), 3.11 (d, *J*= 7.2 Hz, 2H), 1.96-1.83 (m, 1H), 1.52-1.12 (m, 11H), 0.96-0.77 (m, 6H). Residual absorptions side-products: 3.22 (1,6- or 1,8-addition, dd, *J*= 7.5 Hz, 1.6 Hz, 2H), 2.54-2.43 (1,4-addition, m, 1H), 2.43-2.22 (1,4-addition, m, 2H), 2.08 (1,4-addition, q, *J*= 6.8 Hz, 2H); GCOSY ^{1}H NMR: Coupling between the NMR signals at 2.52 ppm and 2.30 ppm and the coupling between the NMR signals at 5.43 and 2.52 ppm indicate 1,4-addition product, Coupling between the NMR signals at 5.55 ppm and 3.21 ppm indicate either 1,6- or 1,8-addition product, Coupling between the NMR signals at 5.44 ppm and 1.80 ppm and the coupling between the NMR signals at 5.77 and 3.10 ppm indicate 1,10-addition product; ^{13}C NMR δ 172.52 (1,4-addition, C), 171.59 (1,10-addition, C), 140.35 (1,10-addition, CH), 135.65 (1,4-addition, CH), 135.01 (1,4-addition, CH), 133.89 (1,10-addition, CH), 133.01 (1,10-addition, CH), 131.77 (1,4-addition, CH), 131.13 (1,4-addition, CH), 130.33 (1,4-addition, CH), 130.27 (1,4-addition, CH), 129.99 (1,10-addition, CH), 129.51 (1,10-addition, CH), 124.11 (1,10-addition, CH), 60.66 (1,10-addition, CH_2), 60.16 (1,4-addition, CH_2), 44.79 (1,10-addition, CH), 41.24 (1,4-addition, CH), 40.14 (1,4-addition, CH_2), 38.28 (1,10-addition, CH_2), 34.69 (1,10-addition, CH_2), 32.45 (1,4-addition, CH_2), 31.45 (1,4-addition, CH_2), 29.54 (1,10-addition, CH_2), 28.05 (1,10-addition, CH_2), 27.73 (1,4-addition, CH_2), 22.81 (1,10-addition, CH_2), 22.19 (1,4-addition, CH_2), 14.27 (1,4-addition, CH_3), 14.18 (1,10-addition, CH_3), 14.05 (1,10-addition, CH_3), 13.89 (1,4-addition, CH_3), 11.74 (1,10-addition, CH_3), 11.53 (1,4-addition, CH_3); MS *m/z* 264 (M^+, 40), 133 ($C_{10}H_{13}$, 82), 119 (C_9H_{11}, 77), 105 (C_8H_9, 67), 93 (C_7H_9, 50), 91 (C_7H_7. 100); HRMS calcd. for $C_{17}H_{29}O_2$ 265.2162, found 265.2163 Ee was determined by chiral GC analysis for 2-ethylhexanoic acid,[xvii] column: Chiraldex-B-PM, 50 °C to 120 °C in 7 min, 120 °C for 70 min; retention times (min): 42.0 (major), 44.0 (minor). Regioselectivity was determined by ^{1}H NMR with d1=10 s.

(*R*,3*E*,5*E*,7*E*)-S-ethyl 9-methyltrideca-3,5,7-trienethioate (**3.81m**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition, 48 h reaction time, 10% catalyst.
[0.5 mmol scale, 82% conversion, 44% yield (combined yield 1,10- and 1,4-addition products), 1,10-product 45% ee, 1,10:1,4 59:41, colorless oil]
$[\alpha]_D^{20}$= −13.4 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 6.23-5.96 (m, 4H), 5.76-5.51 (m, 2H), 3.30 (d, *J*= 7.3 Hz, 1H), 2.91-2.82 (m, 2H), 2.21-2.12 (m, 1H), 1.41-1.17 (m, 9H), 0.99 (d, *J*= 6.7 Hz, 3H), 0.93-0.84 (m, 3H), Residual absorptions 1,4-product: 2.82-2.74 (m, 1H), 2.53 (ddd, *J*= 36.9 Hz, 14.5 Hz, 7.2 Hz, 2H), 2.12-2.04 (m, 2H) , 1.06 (d, *J*= 6.7 Hz, 1H); Coupling between the NMR signals at 2.78 ppm and 2.52 ppm and the coupling between the NMR signals at 5.54 and 2.78 ppm indicate 1,4-addition product, Coupling between the NMR signals at 5.61 ppm and 2.16 ppm and the coupling between the NMR signals at 5.65 and 3.30 ppm indicate 1,10-addition product; ^{13}C NMR δ 198.26 (1,4-addition, C), 197.66 (1,10-addition, C), 142.13 (1,10-addition, CH), 136.82 (1,4-addition, CH), 135.24 (1,10-addition, CH), 135.09 (1,4-addition, CH), 133.61 (1,10-addition, CH), 132.04 (1,4-addition, CH), 130.25 (1,4-addition, CH), 130.22 (1,4-addition, CH), 129.56 (1,4-addition, CH), 129.49 (1,10-addition, CH), 128.25 (1,10-addition, CH), 123.40 (1,10-addition, CH), 50.91 (1,4-addition, CH_2), 47.67, 36.93 (1,10-addition, CH), 36.69 (1,10-addition, CH_2), 34.29 (1,4-addition, CH), 32.45 (1,4-addition, CH_2), 31.44 (1,4-addition, CH_2), 29.54 (1,10-addition, CH_2), 23.39 (1,10-addition, CH_2), 23.30 (1,4-addition, CH_2), 22.78 (1,10-addition, CH_2), 22.32 (1,4-addition, CH_2), 22.19 (1,10-addition, CH_2), 20.45 (1,4-addition, CH_3), 19.86 (1,10-addition, CH_3), 14.76 (1,4-addition, CH_3), 14.63 (1,10-addition, CH_3), 14.05 (1,10-addition, CH_3), 13.89 (1,4-addition, CH_3); MS *m/z* 266 (M^+, 22), 93 (C_7H_9, 100), 91 (C_7H_7. 53),79 (C_6H_7, 44), 77 (C_6H_5. 33); HRMS calcd. for $C_{16}H_{27}OS$ 267.1777, found 267.1779; Ee was determined by chiral GC analysis for 2-methylhexanoic acid,[xvii] column: Chiraldex-B-PM, 50 °C to 130 °C in 8 min, 130 °C for 70 min; retention times (min): 22.6 (minor), 23.8 (major). Regioselectivity was determined by ^{1}H NMR with d1=10 s.

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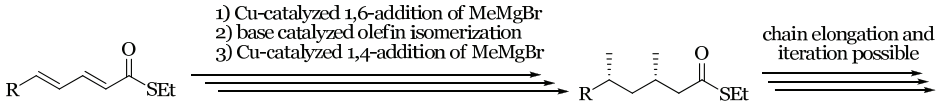
Chapter 4

An Enantioselective Catalytic Approach to *syn* Deoxypropionate Units Combining Asymmetric Copper-Catalyzed 1,6- and 1,4-Conjugate Addition

A novel iterative approach to the synthesis of the naturally ubiquitous syn deoxypropionate motif is described in this chapter. The route featureses a new Horner-Wadsworth-Emmons reagent to prepare α,β,γ,δ-bisunsaturated thioesters. Next, two Me-substituents are introduced in high yield, regio- and enantioselectivity using sequential asymmetric Cu-catalyzed 1,6-conjugate addition, base catalyzed olefin isomerization and Cu-catalyzed enantioselective 1,4-conjugate addition. After reduction to the corresponding aldehyde these transformations can be repeated to install three or more Me groups with a syn 1,3-relationship.



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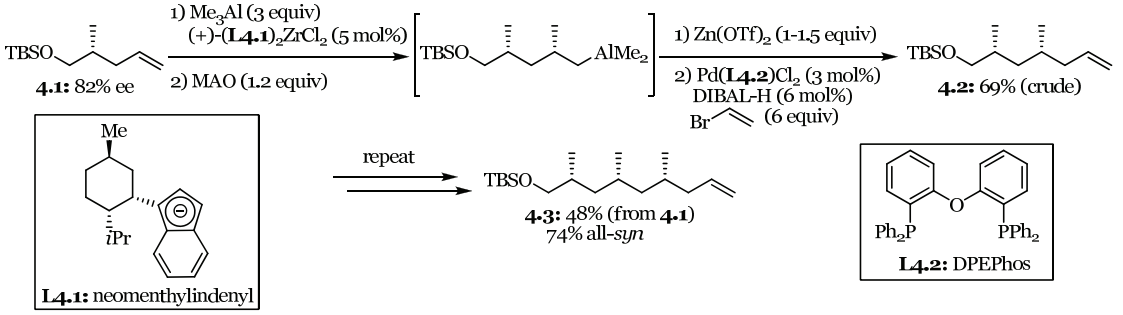
Special issue Henri B. Kagan**:** An 80th Birthday Celebration.

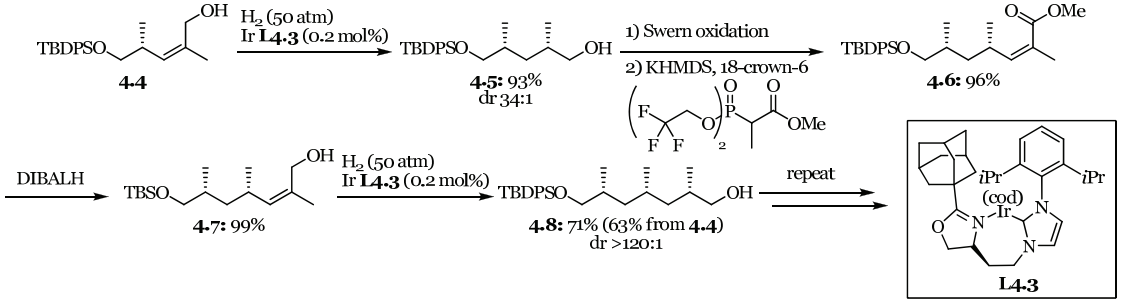
4.1 Enantioselective synthesis of deoxypropionate units

Enantioselective synthesis of the biologically relevant polydeoxypropionate motif has been a topic of intensive research in recent years.[1] As a consequence, a number of highly efficient catalytic iterative methods have been developed.[1] Especially, the methods based on asymmetric Zr-catalyzed carboalumination (Scheme 4.1),[2] as well as iterative Ir-catalyzed hydrogenation[3] (Scheme 4.2) and asymmetric Cu-catalyzed conjugate addition (1,4-ACA, Scheme 4.3)[4,5] have been employed successfully to synthesize a variety of biologically relevant lipids.[6]

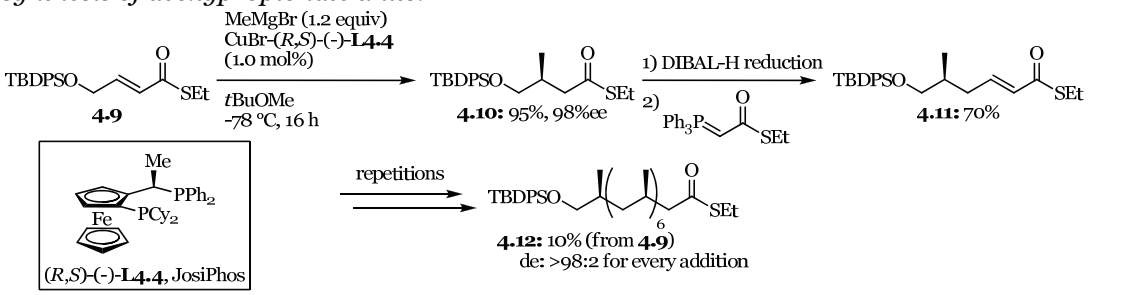
Scheme 4.1. Synthesis of deoxypropionate units with asymmetric Zr-catalyzed carboalumination as key step.



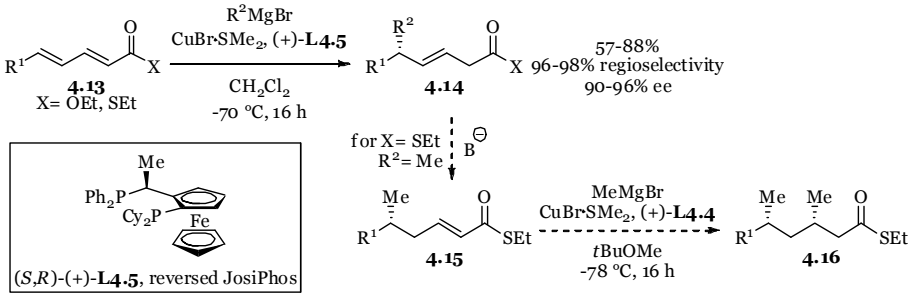
Scheme 4.2. *Synthesis of the deoxypropionate motif using Ir-catalyzed asymmetric hydrogenation as key step.*



Scheme 4.3. *Use of the Cu-catalyzed asymmetric 1,4-addition as key step for the synthesis of deoxypropionate units.*



Scheme 4.4. *Asymmetric catalytic 1,6-addition and envisioned route to deoxypropionate units.*

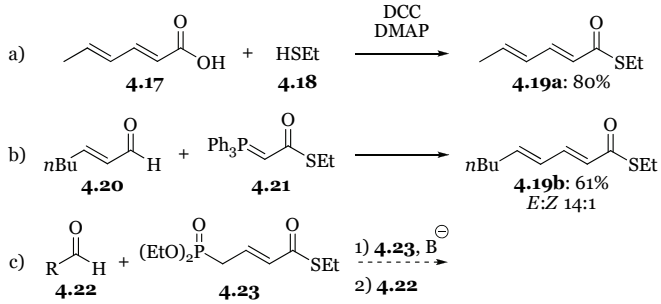


Although the described methods feature high enantioselectivity in combination with low catalyst loading and high yield, alternative routes are still highly warranted. Recently, we reported the asymmetric catalytic 1,6-addition[7] (1,6-ACA) providing access to δ-substituted β,γ-unsaturated esters and thioesters (**4.14**, Scheme 4.4). We envisioned that subsequent isomerization to the α,β-unsaturated thioester **4.15** followed by 1,4-ACA[4] would provide an efficient route to construct 1,3-dimethyl arrays (**4.16**). Here, we describe the combined use of 1,6-ACA[7] and 1,4-ACA[4] in a new protocol for the construction of deoxypropionate subunits.

4.2 Synthesis of α,β,γ,δ-bisunsaturated thioesters

A first prerequisite for a straight-forward route to deoxypropionate units is facile access to α,β,γ,δ-bisunsaturated thioesters (Scheme 4.5). Current methods for the synthesis of α,β,γ,δ-bisunsaturated thioesters comprise thioesterification of an α,β,γ,δ-bisunsaturated acid (route a),[8] as well as Wittig olefination of α,β-unsaturated aldehydes (route b).[9,10] However, only a limited number of α,β,γ,δ-bisunsaturated acids and α,β-unsaturated aldehydes are commercially available. For our envisioned iterative route to deoxypropionate units the development of the novel extended Horner-Wadsworth-Emmons (HWE) reagent **4.23** is required. Coupling of **4.23** with an aldehyde (**4.22**) would provide a general route to a variety of α,β,γ,δ-bisunsaturated thioesters (route c).

Scheme 4.5. *Synthetic routes to α,β,γ,δ-bisunsaturated thioesters.*[a]



[a] Conditions: route a: **4.17**, **4.18** (1.3 equiv), DCC (1.05 equiv), DMAP (0.1 equiv) in CH_2Cl_2 (0.22 M in **4.17**), 0 °C to rt, 16 h; route b: **4.20**, **4.21** (1.3 equiv) in CH_2Cl_2 (0.14 M in **4.20**), 40 °C, 20 h.

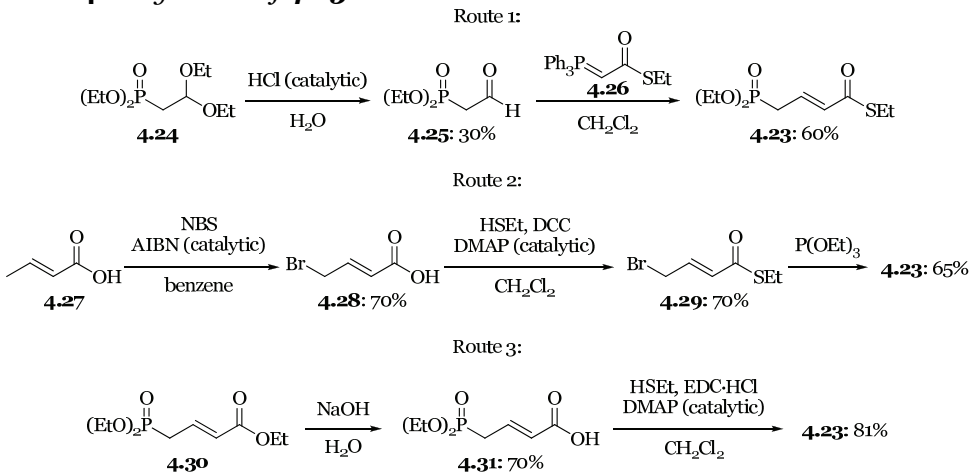
4.3 Synthesis of the thioester extended HWE-reagent

For the preparation of the novel extended HWE-reagent **4.23** several synthetic routes were envisioned (Scheme 4.6). A first route started with the liberation of the aldehyde from the commercially available phosphonate acetal **4.24** (route 1). Acid catalyzed hydrolysis gave **4.25** in low unoptimized yield. Subsequent coupling of **4.25** with the Wittig reagent **4.26** gave the HWE reagent **4.23** in reasonable yield. After purification, traces of triphenylphosphine oxide were still present and due to this impurity this synthetic route was abandoned.

A second approach started with radical bromination of crotonic acid (**4.27**) which gave 4-bromocrotonic acid (**4.28**), after several recrystallizations, in good yield (route 2). Subsequent thioesterification yielded **4.29**. Finally, **4.29** was converted to the HWE reagent **4.23** by an Arbuzov reaction. At 120 °C the Arbuzov reaction gave poorly reproducible results (Table 4.1, entry 1). With a slightly extended reaction time at 100 °C a reproducible yield of 65% was obtained (entry 2). Performing the reaction at 80 °C gave lower yield (entry 3). Again, purification proved challenging and along with the HWE reagent **4.23** traces of triethylphosphate were obtained.

For the third synthetic route the, in technically grade commercially available, triethyl 4-phosphonocrotonate was purified to give pure *E*-**4.30** (Scheme 4.6, route 3). Subsequent saponification provided phosphonate acid **4.31** in reasonable yield. Finally, thioesterification using EDC•HCl[i] provided the pure HWE reagent **4.23**.

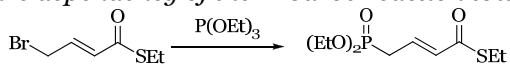
Scheme 4.6. *Synthesis of* ***4.23***.[a]



[a] Conditions: **4.24** in an aq HCl solution (1%, 0.15 M in **4.24**), rt, 8 h; **4.25**, **4.26** (1.3 equiv) in CH_2Cl_2 (0.1 M in **4.26**), 40 °C, 48 h; **4.27**, NBS (1.1 equiv), AIBN (3 mol%) in benzene (1.2 M in **4.27**), 80 °C, 2 h; **4.28**, HSEt (1.3 equiv), DCC (1.05 equiv), DMAP (10 mol%) in CH_2Cl_2 (0.18 M in **4.28**), 0 °C to rt, 16 h; **4.29** in neat $P(OEt)_3$ (1.4 equiv), 100 °C, 0.5 h; **4.30**, NaOH (1.3 equiv) in 0.23 mL H_2O (0.24 M in **4.30**), 3 h; **4.31**, HSEt (1.0 equiv), EDC•HCl (1.1 equiv), DMAP (10 mol%) in CH_2Cl_2 (0.18 M in **4.31**), 0 °C to rt, 16 h.

[i] The use of DCC for this coupling gave problems during purification. The product and the formed DCU proved difficult to separate.

Table 4.1. *Temperature dependency of the Arbuzov reaction towards* ***4.23***.[a]



4.29 **4.23**

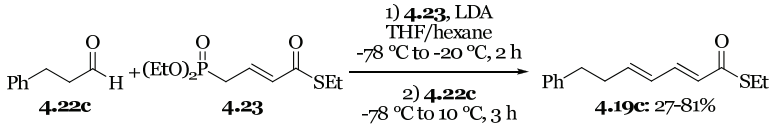
entry	temperature	reaction time	yield[b]
1	120 °C	15 min	25-75%
2	100 °C	30 min	65%
3	80 °C	60 min	40%

[a] Conditions: **4.29** in neat $P(OEt)_3$ (1.4 equiv). [b] **4.29** was completely converted in all cases.

4.4 Synthesis of α,β,γ,δ-bisunsaturated thioesters with the extended HWE reagent

Initially, the HWE reaction with hydrocinnamaldehyde **4.22c** was chosen as test reaction. The coupling of the HWE reagent **4.23** and this particular aldehyde gave poorly reproducible results with yields ranging from 27-80% (Scheme 4.7). To obtain better reproducibility the deprotonation step was investigated (Table 4.2). Deprotonation of **4.23** with several Li-bases, LDA (entry 1), *n*BuLi (entry 2) or LHMDS (entry 3, 4), allowed, after subsequent quenching, the recovery of **4.23** with only traces of degradation products. However, by deprotonation with NaH and subsequent quenching at low temperature only trace amounts of **4.23** were recovered (entry 5). To further study the reaction, LHMDS was chosen as the base of choice. The use of LHMDS allows the HWE-reactions to be performed at low temperature. Furthermore, the use of LHMDS gives a sterically encumbered amine as side-product, limiting the role of this amine in further side-reactions. Furthermore, the low reproducibility in our study and low yield reported in a related study[11] when hydrocinnamaldehyde (**4.22c**) was used as coupling partner, prompted us to further perform optimization using isobutyraldehyde (**4.22d**).

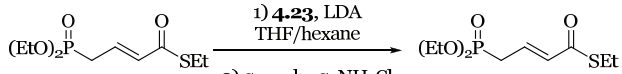
Scheme 4.7. *Reproducibility of the HWE reaction with reagent* ***4.23***.[a]



4.22c **4.23** **4.19c**: 27-81%

[a] Conditions: 1) **4.23** (1.43 equiv), LDA (1.4 equiv), THF (0.13 M in **4.23**), −78 to −20 °C, 3 h, then 2) **4.22c**, THF (total 0.074 M in **4.22c**).

Table 4.2. *Stability of* ***4.23*** *under basic conditions*.[a]



4.23 **4.23**

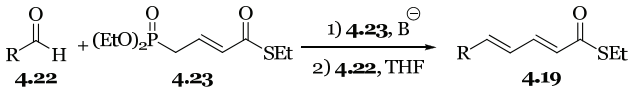
entry	base	temperature	reaction time	recovery of **4.23**
1	LDA	−78 to −20 °C	20 min	>95%
2	*n*BuLi	−78 °C to rt	30 min	>95%
3	LHMDS	−78 °C	30 min	>95%
4	LHMDS	−40 °C	30 min	>95%
5	NaH	−78 to −20 °C	20 min	<20%

[a] Conditions: 1) **4.23** (1.43 equiv), LDA (1.4 equiv), THF (0.13 M in **4.23**), then 2) 1 M aq NH_4Cl solution (excess).

Using isobutyraldehyde **4.22d** and the conditions reported for the extended HWE reaction[12] with the oxoester analogue of **4.23**,[13] the product **4.19d** was obtained in modest, poorly reproducible yields but excellent *E*/*Z*-selectivity (Table 4.3, entry 1). The use of LHMDS as base improved the yield slightly but still gave poorly reproducible results (entry 2 and 3). Optimization of the reaction conditions identified that strict temperature control (addition of aldehyde at −78 °C and allowing the reaction mixture to warm up in 30 min to −40 °C) in combination with high dilution conditions (0.039 M in **4.22d**) for the reaction were essential to give **4.19d** in good and reproducible yield and excellent *E*/*Z*-selectivity (entry 4).[ii] Addition of the aldehyde at −40 °C gave the same result (entry 5). In contrast, when the reaction was performed at higher temperature (−30 °C to rt) and higher concentration, a low yield was obtained (entry 6). The reason for the low yield is unclear and the formed side-products could not be characterized. However, the aldehyde is presumably involved in a side-reaction since the reaction with an excess of aldehyde at higher concentration led to extremely low yield (entry 7).

Using the optimized conditions, the functionalized aldehydes **4.22c** and **4.22e** were converted and the desired α,β,γ,δ-bisunsaturated thioesters **4.19c** and **4.19e** were obtained in lower, but acceptable, yields (entry 8, 9). Presumably, the more accessible α-H of **4.22c** and **4.22e** compared to the sterically encumbered α-H in **4.22d** causes side-reactions to occur. Finally, DIBAL-H reduction and extended HWE reaction of **4.32**[iii] provided the chiral 1,6-ACA substrate **4.19f** in 64% yield over 2 steps (Scheme 4.8).

Table 4.3. *HWE reaction leading to α,β,γ,δ-bisunsaturated thioesters.*[a]



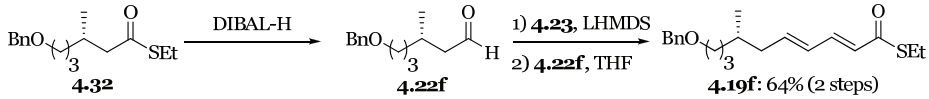
entry	aldehyde	product	base	conditions step 2	molarity (M)	yield[b]
1	**4.22d**; R=*i*Bu	**4.19d**	LDA	−78 °C to rt, 3 h	0.074 M	50%[c]
2	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−78 to −20 °C, 16 h	0.29 M	70%[d]
3	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−78 to −40 °C, 16 h	0.29 M	70%[d]
4	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−78 to −40 °C, 16 h	0.039 M	70%
5	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−40 °C, 16 h	0.039 M	70%
6	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−30 °C to rt, 3 h	0.29 M	35%
7[e]	**4.22d**; R=*i*Bu	**4.19d**	LHMDS	−30 °C to rt, 3 h	0.29 M	<15%
8	**4.22c**; R=CH_2Bn	**4.19c**	LHMDS	−78 to −40 °C, 16 h	0.039 M	39%
9	**4.22e**; R=$(CH_2)_3$OBn	**4.19e**	LHMDS	−78 to −40 °C, 16 h	0.039 M	47%

[a] Conditions: entry 1: 1) **4.23** (1.43 equiv), LDA (1.4 equiv), THF (0.13 M in **4.23**), −78 to −20 °C, 3 h, then 2) **4.22d**, THF (total 0.074 M in **4.22d**); entry 2, 3 and 6: **4.23** (1.5 equiv), LHMDS (1.4 equiv), THF (0.63 M in **4.23**), −78 °C, 0.5 h, then 2) **4.22d**, THF (total 0.29 M in **4.22d**); entry 4, 5, 8 and 9: **4.23** (1.5 equiv), LHMDS (1.4 equiv), THF (0.07 M in **4.23**), −78 °C, 0.5 h, then 2) **4.22**, THF (total 0.039 M in **4.22**); entry 7: **4.23** (1.5 equiv), LHMDS (1.4 equiv), THF (0.63 M in **4.23**), −78 °C, 0.5 h, then 2) **4.22d** (7.5 equiv), THF (total 0.29 M in **4.22d**). [b] In all cases the products were obtained with over 95:5 *E*:*Z*-ratio according to ^{1}H-NMR. [c] Yields in the range of 30 to 50% were obtained. [d] Yields in the range of 30 to 70% were obtained. [e] **4.22d** (7.5 equiv) was used and the reported yield is based on the HWE reagent **4.23**.

[ii] All reported yields are for reactions at 0.5 mmol scale. The reaction was performed at larger scale with the conditions reported for entry 3 and gave low yield (~30%). Presumably strict control of the temperature is needed to obtain good yields at larger scale.

[iii] For the synthesis of **4.32** see experimental section.

Scheme 4.8. *Synthesis of the chiral 1,6-ACA substrate* ***4.19f****.*[a]



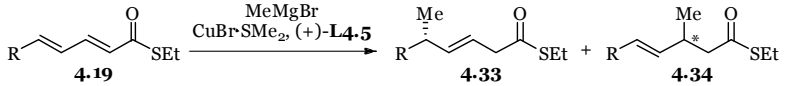
4.32 **4.22f** **4.19f**: 64% (2 steps)

[a] Conditions: reduction: **4.32**, DIBAL-H (1.2 equiv), CH_2Cl_2 (0.29 M in **4.32**), −75 °C, 3 h; extended HWE reaction: see Table 4.3, entry 4, 5, 8 and 9.

4.5 Asymmetric 1,6-addition of MeMgBr to α,β,γ,δ-bisunsaturated thioesters

With the substrates in hand, the scope of the 1,6-ACA[7] of MeMgBr[iv] was explored (Table 4.4). Employing CuBr•SMe_2 and (+)-reversed JosiPhos (**L4.5**), the 1,6-ACA of MeMgBr to substrate **4.19b** proceeds in high yield and excellent regio- and stereoselectivity (entry 1). When the more bulky ζ-Me substituted substrate **4.19c** was subjected to 1,6-ACA, a slight drop in regio- and enantiocontrol was observed (entry 2). This drop in regio- and enantioselectivity is a continuing trend; for the more sterically encumbered R-groups both enantio- and regioselectivity for the 1,6-ACA are lower.[v] The substrates incorporating a phenyl or benzyloxy functionality gave good yields and good to excellent regio- and stereocontrol (entries 3 and 4). Finally, the ability of the catalyst to override substrate control[14] was tested by the 1,6-ACA of MeMgBr to chiral substrate **4.19f**. *Syn*-addition proceeded in high yield, regio- and diastereoselectivity (entry 5), while *anti*-addition, using the enantiomer of **L4.5**, gave high yield and regioselectivity, but moderate diastereoselectivity (entry 6).

Table 4.4. *1,6-ACA to α,β,γ,δ-bisunsaturated thioesters.*[a]



4.19 **4.33** **4.34**

entry	substrate	product	yield[b] (%)	**4.33**: **4.34**[c]	ee (%)[d]
1	**4.19b**, R= *n*Bu	**4.33b**	83	99:1[e]	89
2	**4.19c**, R= *i*Bu	**4.33c**	84	95:5	82
3	**4.19d**, R= CH_2Bn	**4.33d**	78	99:1[e]	82
4	**4.19e**, R= $(CH_2)_3OBn$	**4.33e**	86	94:6	86
5[f]	**4.19f**, $CH_2((R)\text{-}CHMe)(CH_2)_3OBn$	**4.33f**	88	85:15	(87:13)[g]
6[h]	**4.19f**, $CH_2((R)\text{-}CHMe)(CH_2)_3OBn$	**4.33g**	83	87:13	(22:78)[g]

[a] Conditions: **4.19** in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**L4.5** (5.25 mol%) and CuBr•SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **4.19**), −70 °C, 16 h. [b] Yields include both **4.33** and **4.34**. [c] Ratio **4.33**:**4.34** was determined by ^{1}H-NMR. [d] Enantioselectivity was determined by chiral GC or HPLC. [e] Ratio **4.33**:**4.34** was determined by chiral GC or HPLC. [f] **4.19f** was prepared in 93% ee. [g] Diastereoselectivity *syn*:*anti*. [h] **4.19f** was prepared in 93% ee, (−)-**L4.5** was used.

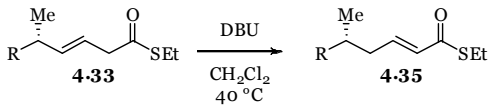
[iv] A limitation of the current method was discovered when **4.19a** was subjected to 1,6-ACA of the more reactive EtMgBr or *n*BuMgBr leading to the 1,6-addition products in high yield and regioselectivity but moderate enantioselectivity (see also paragraph 2.6).

[v] This trend is even more apparent when the results in Table 4.4 are compared to the results of 1,6-ACA to the R=Et substituted α,β,γ,δ-bisunsaturated thioester reported in reference 7/paragraph 2.6 (93% ee and 97% regioselectivity).

4.6 Isomerization of β,γ-unsaturated thioesters to α,β-unsaturated thioesters

For the next step in the iterative sequence, the isomerization to the α,β-unsaturated thioester **4.35**, a variety of methods was investigated. The olefin was resistant to isomerization by heat (xylene, 140 °C) and various transition metal catalysts ($Pd(OAc)_2$, $Pd(PPh_3)_4$, Wilkinson's catalyst and $RuCl_3$). Base-catalyzed isomerization employing DBU was more effective[vi] to isomerize the double bond into the desired position (Table 4.5, entry 1 and 2). Optimization of the amount of DBU used for this transformation identified that 5 equiv of DBU was optimal for isomerization in 16 h (entry 3).[vii] Employing the conditions described in entry 3, the α,β-unsaturated product **4.35** was obtained without racemization of the stereogenic Me-center.[viii] Use of more DBU did not lead to full isomerization (entry 4, 5). Furthermore, exposing isolated α,β-unsaturated thioester **4.35d** once more to the reaction conditions gave a mixture of β,γ-unsaturated thioester **4.33d** and α,β-unsaturated thioester **4.35d** (entry 6); indicating an equilibrium.

Table 4.5. *Isomerization of β,γ-unsaturated thioester **4.33** to α,β-unsaturated thioester **4.35**.*[a]



entry	substrate	product	equiv DBU	reaction time	**4.33**: **4.35**[b]	yield[c] (%)
1	**4.33b**; R= *n*Bu	**4.35b**	0.1	16 h	50:50	88
2	**4.33b**; R= *n*Bu	**4.35b**	1.5	16 h	20:80	87
3	**4.33b**; R= *n*Bu	**4.35b**	5	16 h	12:88	88
4	**4.33b**; R= *n*Bu	**4.35b**	10	16 h	12:88	88
5	**4.33b**; R= *n*Bu	**4.35b**	10	64 h	15:85	90
6	**4.35d**; R= CH_2Bn[d]	**4.35d**	5	16 h	11:89	n. d.

[a] Conditions: **4.33** or **4.35** and DBU in CH_2Cl_2 (0.1 M in **4.33** or **4.35**), 40 °C. [b] Ratio of **4.33**:**4.35** was determined by GC-MS. [c] Yields reported are combined yields for **4.33**, **4.35** and the traces of **4.34** present from the 1,6-ACA. [d] Pure isolated **4.35d** was used.

4.7 Iterative synthesis of deoxypropionate units

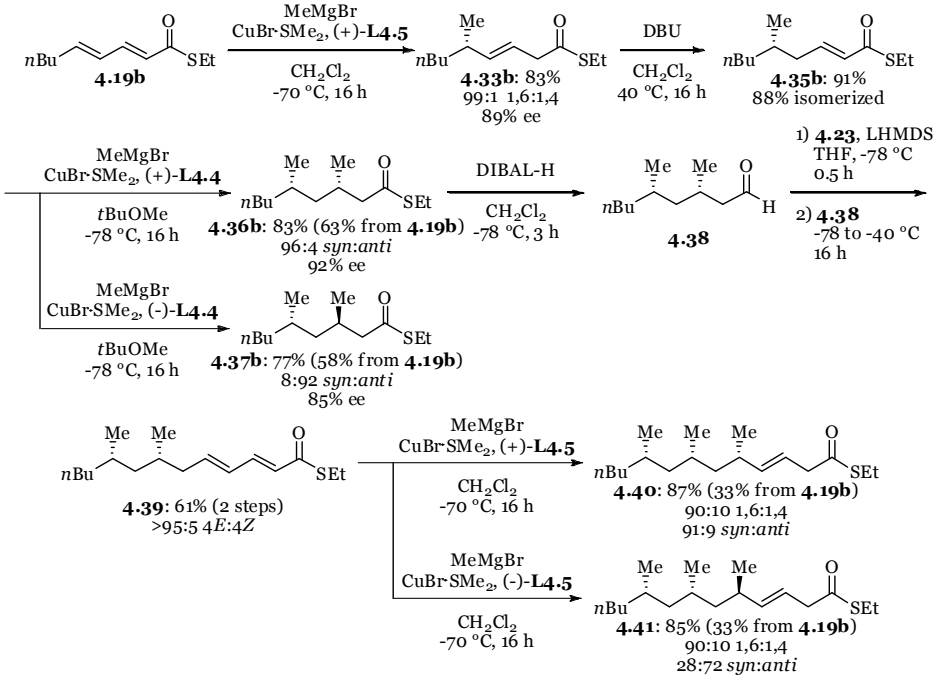
To test our alternative synthetic strategy for the iterative construction of deoxypropionate units, several Me-centers starting from **4.19b** were introduced (Scheme 4.9). Both the *syn*- (**4.36b**) and *anti*-product (**4.37b**), incorporating two

[vi] The use of an excess of NEt_3 for this isomerization only resulted in starting material **4.33d**.

[vii] Due to the hydrophobic nature of the obtained products, attempts to separate the two regioisomers were unsuccessful. Fortunately, the presence of these impurities did not affect the subsequent 1,4-ACA.

[viii] The conversion of **4.33d** to **4.35d** did not give any racemization as was established using chiral HPLC (see experimental section).

Scheme 4.9. *Iterative construction of deoxypropionate units starting from* ***4.19b***.[a,b]



[a] Conditions: 1,6-ACA: see Table 4.4; isomerization: see Table 4.5; 1,4-ACA: **4.35b** in tBuOMe was added to a solution of MeMgBr (3.0 M in Et_2O, 1.5 equiv) and **L4.4**-CuBr•SMe_2 complex (1.0 mol%) in tBuOMe (0.2 M in **4.35b**), −78 °C, 16 h; Reduction and chain elongation: see Scheme 4.8; 1,6-ACA: see Table 4.4. [b] Yield for the 1,6-ACA includes **4.33b** and **4.34b**; Yield for the isomerization step includes **4.33b**, **4.34b** and **4.35b**; Yield for the subsequent 1,4-ACA includes only **4.36b** and **4.37b**.

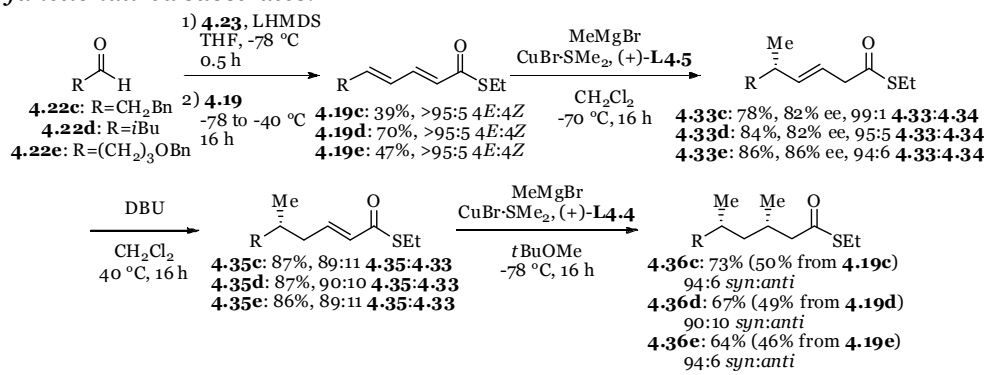
Me-substituents, were obtained in good regio- and stereoselectivity and overall yield (63% and 58% over three steps respectively).[ix,x] Subsequent chain elongation gave the 1,6-ACA substrate **4.39** in good yield and excellent *E*:*Z* ratio. Finally, synthesis of the *syn*,*syn*-1,6-ACA product **4.40** proceeded in good yield, regio- and diastereoselectivity while the formation of the *syn*,*anti*-1,6-ACA product **4.41**, upon switching of the ligand chirality in the final 1,6-addition, proceeded in good yield and regioselectivity but mediocre diastereoselectivity.

The general nature of the construction of deoxypropionate units via consecutive 1,6-ACA- isomerization- 1,4-ACA was illustrated by the introduction of two consecutive methyl groups on several functionalized substrates (Scheme 4.10, next page). In all cases the products comprising two deoxypropionate units were obtained in good yield, regio- and diastereoselectivity.

[ix] The lower enantio- and diastereoselectivity of the 1,4-ACA on **4.34b** compared to the results reported in ref 4d can be explained by the lower ee of **4.34b** (89% ee vs 95% ee).

[x] Although separation of **4.33b**, the 1,4-addition side-product of the 1,6-ACA (**4.34b**) and **4.35b** in earlier stages of the synthesis was not possible, at this stage the pure mixture of the saturated products **4.36b** and **4.37b** was obtained successfully.

Scheme 4.10. *Iterative construction of deoxypropionate units on several functionalized substrates.*[a,b]



[a] Conditions: extended HWE: see Table, 4.3 entry 4, 5, 8 and 9; 1,6-ACA: see Table 4.4; isomerization: see Table 4.5; 1,4-ACA: see Scheme 4.9. [b] Yield for the 1,6-ACA include **4.33** and **4.34**; yield for the isomerization step include **4.33**, **4.34** and **4.35**; Yield for the subsequent 1,4-ACA include only *syn*-**4.36** and *anti*-**4.37**.

4.8 Conclusion

In summary we have developed an alternative method for the construction of deoxypropionate units exploiting Cu-catalyzed 1,6-ACA[7] and 1,4-ACA.[4d] To allow iterative construction of deoxypropionate units, a novel method for the construction of α,β,γ,δ-bisunsaturated thioesters and an alternative method for the construction of α,β-unsaturated thioesters were developed. The novel route was used for the iterative construction of several Me-centers in a *syn*-1,3-fashion and the corresponding products were obtained in good yield, regio- and enantioselectivity. It must be emphasized that the current methodology is suited for the construction of *syn*-deoxypropionate units; while the *anti*-deoxypropionate units are presumably constructed more efficiently by the 1,4-ACA.[4d]

4.9 Perspective and outlook

A fair comparison of the different synthetic methods to prepare *syn* deoxypropionate units is difficult to make and is highly dependent on the warranted target product. However, a comparison for representative examples using the different methods (Scheme 4.1, Scheme 4.2, Scheme 4.3 and Scheme 4.9) for the *syn*-selective introduction of the second Me-center is given in Table 4.6. The data in Table 4.6 is also representative for the *syn*-selective formation of further Me-centers. The average yield for the introduction of a single Me-center is between 60 and 65%; with the method using asymmetric Zr-catalyzed carboalumination and the method described in this chapter giving a slightly lower average yield. In view of the number of synthetic steps for the construction of a single stereogenic center the method using asymmetric Zr-catalyzed carboalumination and the method described in this chapter are the preferred methods.

Table 4.6. *Comparison of several synthetic methods for the formation of a single syn deoxypropionate unit.*

entry	method	number of steps	ee SM (%)	average yield (%)[a]	de product
1	Zr-catalyzed carboalumination[2]	2	82	~60[b]	87:13
2	Ir-catalyzed hydrogenation[3]	4	>99	~65	>120:1
3	Cu-catalyzed 1,4-ACA[4]	3	98	~65	>98:2
4	Cu-catalyzed 1,6-ACA and 1,4-ACA	2.5[c]	89	~60	96:4

[a] Average yield for exclusively the *syn* product. [b] 74% average yield of a 87:13 mixture of *syn* and *anti* product was obtained. [c] 5 steps required for the construction of two *syn* deoxypropionate units.

The method relying on Cu-catalyzed 1,6-ACA and 1,4-ACA as key step still has a number of drawbacks. One of these drawbacks is the slightly lower enantioselectivity obtained for the 1,6-ACA of MeMgBr to α,β-unsaturated thioesters compared to the corresponding enantioselectivities for the 1,4-ACA.[4d] This drawback is readily circumvented by the construction of the first stereogenic center by 1,4-ACA,[4d] subsequent chain elongation and 1,6-ACA taking advantage of the inherent preference[14] for the formation of *syn* deoxypropionate units. Another drawback of the method described here is the inherent difficulty of working with mixtures for several steps, complicating analysis. Probably, when more polar substrates are used for 1,6-ACA and base-catalyzed isomerization, separation of the intermediate products will be possible. A final drawback of the described method is the low yields encountered on scale up of the synthesis of α,β,γ,δ-bisunsaturated thioesters using the extended thioester HWE reagent. Certainly this particular HWE reaction needs further optimization.

To further improve the current method, especially, the enantioselectivity for the 1,6-ACA to α,β,γ,δ-bisunsaturated thioesters should be improved. Preliminary results gave a similar enantioselectivity and regioselectivity for the Cu-catalyzed 1,6-ACA using JosiPhos as ligand (in contrast to the use of the same ligand for the 1,6-ACA to α,β,γ,δ-bisunsaturated oxoesters reported in chapter 2). So, possibly further screening of JosiPhos-type ligands might identify a ligand which will yield the 1,6-ACA products in higher ee. Finally, further studies on the HWE reaction using the extended thioester reagent are needed to improve the yield for these transformations and to allow the reaction to be scaled up. Especially, characterization of the side-products with high molecular mass by LC-MS might suggest ways to improve the HWE reaction with this particular HWE reagent.

With these small improvements the route for the iterative introduction of stereogenic methyl centers described in this chapter can become one of the methods of choice for the iterative construction of *syn* deoxypropionate units.

4.10 Acknowledgment

D. J. van Dijken is acknowledged for most of the results presented in paragraphs 4.3 and 4.4.

4.11 Experimental section

General procedures:
All reactions under N_2 atmosphere were conducted using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under a N_2 atmosphere prior to use. *t*BuOMe was distilled from CaH_2 under a N_2 atmosphere prior to use. CuBr•SMe_2 was purchased from Sigma-Aldrich. (+)-(*S*,*R*)-reversed Josiphos, (−)-(*R*,*S*)-reversed Josiphos, (+)-(*S*,*R*)-Josiphos and (−)-(*R*,*S*)-Josiphos were purchased from Sigma-Aldrich. For Josiphos the previously prepared CuBr complexes were used.[4c] MeMgBr was purchased from Sigma-Aldrich and was titrated using *s*BuOH and catalytic amounts of 1,10- phenanthroline before use.
Diethyl phosphonoacetaldehyde diethyl acetal, crotonic acid, N-bromosuccinimide, EtSH, DCC, triethyl phosphite, sorbic acid, isovaleraldehyde, DBU and DIBAL-H were purchased from Sigma-Aldrich. Azobis(isobutyronitrile) was purchased from Janssen Chimica. DMAP, *E*-2-heptenal and hydrocinnamylaldehyde were purchased from ACROS. EDC-HCl salt was purchased from Fluka.
S-ethyl 2-(triphenylphosphoranylidene)ethanethioate was prepared as described in ref 9. Triethylphosphonocrotonate was purchased from Aldrich (90% technical grade) and purified by column chromatography (gradient Et_2O:pentane 25:75 to Et_2O) to give pure 2*E*-triethylphosphonocrotonate.
Thin-layer chromatography (TLC) was performed on commercial Kieselgel $60F_{254}$ silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by capillary GC analysis (HP6890, Chiraldex-B-PM 30 m x 0.25 mm x 0.25 μm; HP6890, Chiralsil-DEX-CB 25 m x 0.25 mm x 0.25 μm) using flame ionization detection or HPLC (chiralcel OB-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm; chiralcel OJ-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm) (in comparison to authentic samples of racemates of 1,6- and 1,4-addition products). Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent absorptions ($CHCl_3$, δ= 7.26 for hydrogen atoms, δ= 77.16 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a AEI-MS-902 mass spectrometer by EI (70 ev) measurements on a FTMS Orbitrap FischerScientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA).
For spectra see supporting information of the paper mentioned on page 119.

Data in this experimental section is ordered as follows:
1. Synthesis of HWE-reagent **4.23**
2. Synthesis of 1,6-ACA substrates
3. Synthesis of 1,6-ACA products
4. Synthesis of 1,4-ACA substrates
5. Synthesis of 1,4-ACA products

Synthesis of extended Horner-Wadsworth-Emmons reagent **4.23**:
Route 1:[xi]

[xi] This route was only performed on analytical scale.

Unmasking of aldehyde from acetal **4.24**:
In a roundbottom flask equipped with stirring bar, the acetal **4.24** (1.1 mL, 4.6 mmol) was dissolved in an aq 1% HCl solution (30 mL). After stirring at rt for 8 h the reaction mixture was extracted with Et_2O (3x 15 mL). The combined organic extracts were washed with an aq $NaHCO_3$ solution (saturated, 2x 30 mL), dried and concentrated to a colorless oil and the crude product was immediately used for the Wittig reaction.

Diethyl 2-oxoethylphosphonate (**4.25**) data in accordance with data described in ref 15.
~30% yield (unoptimized), colorless oil.

Wittig reaction of **4.25**:
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, S-ethyl 2-(triphenylphosphoranylidene)ethanethioate (**4.26**, 1.49 g, 4.09 mmol, 1.3 equiv) was dissolved in anhydrous CH_2Cl_2 (30 mL). The aldehyde **4.25** (0.57 g, 3.15 mmol, 1.0 equiv) was added, the reaction mixture was heated to reflux and stirred for 48 h, allowed to cool to rt and stirred for 4 d at rt. The reaction mixture was then concentrated and the remaining solid was extracted with pentane (3x 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (gradient EtOAc:pentane 50:50 to EtOAc) yielded **4.23** as a colorless oil with a minor impurity of triphenylphosphine oxide.

E-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (**4.23**):
~60% yield, colorless oil mixed with some white solid.
For spectroscopic data, *vide infra*.

Route 2:
Bromination of crotonic acid (**4.27**): [16]
In a roundbottom flask equipped with a stirring bar, crotonic acid (**4.27**, 20 g, 0.23 mol, 1.0 equiv) and N-bromosuccinimide (46 g, 0.25 mol, 1.1 equiv) were dissolved in benzene (200 mL). After the solution was heated to reflux, azobis(isobutyronitrile) (1.14 g, 6.97 mmol, 3 mol%) was added and heating at reflux temperature was continued for 2 h. Then the reaction solution was cooled to 0 °C and filtered over celite. The residue was washed with toluene (50 mL). The filtrate was concentrated and recrystallized from toluene to yield **4.28** as a white solid in several batches.

(*E*)-4-bromobut-2-enoic acid (4-bromocrotonic acid) (**4.28**):
70% yield, white solid, mp: 74.7-75.3 °C.
^{1}H NMR δ 11.63 (s, br, 1H), 7.10 (dt, *J*= 7.3 Hz, 15.3 Hz, 1H), 6.03 (d, *J*= 15.4 Hz, 1H), 4.01 (d, *J*= 7.3 Hz, 2H), spectrum contains traces of crotonic acid; ^{13}C NMR δ 171.3 (C), 144.65 (CH), 123.99 (CH), 28.86 (CH_2); MS *m/z* 166 (M^+ Br^{81}, 56), 164 (M^+ Br^{79}, 56), 85 (M-Br, 100); HRMS calcd. for $C_4H_5BrO_2$ 163.9473, found 163.9471.

Thioesterification of 4-bromocrotonic acid: [17]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid **4.28** (3.47 g, 21.02 mmol, 1.0 equiv), EtSH (1.55 mL, 21.02 mmol, 1.0 equiv) and DMAP (0.26 g, 2.10 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (120 mL), the solution was cooled to 0 °C and DCC (4.76 g, 23.12 mmol, 1.1 equiv) was added. After addition the reaction mixture was stirred for 16 h at rt. The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were subsequently washed with a saturated aq $NaHCO_3$ solution (150 mL), H_2O (150 mL) and a saturated brine solution (100 mL), dried and concentrated to yield a colorless oil. Flash chromatography (Et_2O:pentane 1:99) provided **4.29** as a colorless oil (3.08 g, 14.7 mmol).

E-S-ethyl 4-bromobut-2-enethioate **4.29**; data in accordance with data described in ref 17.
70% yield, colorless oil.

Arbuzov reaction of **4.29**:
In a roundbottom flask equipped with stirring bar, *E*-S-ethyl 4-bromobut-2-enethioate **4.29** (2.0 g, 9.57 mmol, 1.0 equiv) and triethyl phosphite (2.33 mL, 13.40 mmol, 1.4 equiv) were mixed and warmed in a preheated oil bath at 100 °C. The mixture was stirred for 30 min and then allowed to cool down to rt. Flash column chromatography (EtOAc:pentane 67:33) yielded **4.23** as a light yellow oil.

E-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (**4.23**):
65% yield, light yellow oil.
For spectroscopic data, *vide infra*.

Route 3:
Saponification of triethylphosphonocrotonate **4.30**:
4.31 was obtained via a known procedure.[18]

4-Diethoxyphosphorylbut-2-enoic acid **4.31**; data in accordance with data described in ref 18 (4-diethoxyphosphoryl-2-butenoic acid).
70% yield, colorless oil.

Thioesterification of **4.31**:
In a roundbottom flask equipped with a stirring bar under a N_2 atmosphere, EtSH (3.0 mL, 40.42 mmol 1.0 equiv), 4-diethoxyphosphorylbut-2-enoic acid **4.31** (8.98 g, 40.42 mmol, 1.0 equiv) and DMAP (0.49 g, 4.04 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (100 mL), the solution was cooled to 0 °C and EDC-HCl salt (8.52 g, 44.46 mmol, 1.1 equiv) was added. After addition the reaction mixture was stirred for 16 h at rt. The reaction mixture was then washed with, subsequently, an aq Na_2CO_3 solution (saturated, 3x 100 mL), H_2O (2x 100 mL) and a saturated brine solution (75 mL). The organic extracts were dried and carefully concentrated to a colorless oil. Flash column chromatography (gradient EtOAc:pentane 20:80 to EtOAc) yielded **4.23** as a colorless oil.

(*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (**4.23**):
81% yield, colorless oil.
^{1}H NMR δ 6.85-6.67 (m, 1H), 6.20 (dd, *J*= 15.5 Hz, 4.8 Hz, 1H), 4.20-3.98 (m, 4H), 2.92 (q, *J*= 7.4 Hz, 2H), 2.70 (ddd, *J*= 23.0 Hz, 7.8 Hz, 1.3 Hz, 2H), 1.30 (t, *J*= 7.1 Hz, 6H), 1.25 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 188.83 (C), 133.03 (d, $^2J_{C\text{-}P}$= 11.2 Hz, CH), 132.24 (d, $^3J_{C\text{-}P}$= 13.7 Hz, CH), 62.04 (d, $J_{C\text{-}P}$= 6.6 Hz, CH_2), 30.10 (d, $^2J_{C\text{-}P}$= 138.2 Hz, CH_2), 22.86 (CH_2), 16.11 (d, $^3J_{C\text{-}P}$= 5.9 Hz, CH_3), 14.40 (CH_3); ^{31}P NMR δ 25.13 (t, *J*= 13.6 Hz); MS *m/z* 266 (M^+, 3), 205 (M-SEt, 62), 177 (M-COSEt, 33), 149 ($C_5H_{10}O_3$, 100); HRMS calcd. for $C_{10}H_{19}O_4PS$ 266.0742, found 266.0729.

Synthesis of substrates for 1,6-addition:
Thioesterification of sorbic acid **4.17**:[19]
In a roundbottom flask equipped with stirring bar under N_2 atmosphere, sorbic acid (**4.17**, 1.12 g, 10.0 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (30 mL). Subsequently, DMAP (0.12 g, 1.0 mmol, 0.1 equiv) and EtSH (0.97 mL, 13.0 mmol, 1.3 equiv) were added and the reaction mixture was cooled to 0 °C using an ice bath. Then, DCC (2.17 g, 10.5 mmol, 1.05 equiv) dissolved in anhydrous CH_2Cl_2 (15 mL) was added slowly. After addition the ice bath was removed and the reaction mixture was stirred for 16 h at rt. The reaction mixture was then filtered over celite and the residue was washed with CH_2Cl_2 (50 mL). The combined organic extracts were then subsequently washed with saturated aqueous $NaHCO_3$-solution (50 mL), H_2O (50 mL) and a saturated brine solution (50 mL), dried and concentrated. Flash column chromatography (Et_2O:pentane 2.5:97.5) yielded **4.19a** as a colorless oil.

2*E*,4*E*-S-ethylhexa-2,4-dienethioate (**4.19a**):
80% yield, colorless oil.

^{1}H NMR δ 7.14 (dd, *J*= 15.2 Hz, 10.1 Hz, 1H), 6.22-6.06 (m, 2H), 6.02 (d, *J*= 15.1 Hz, 1H), 2.92 (qd, *J*= 7.4 Hz, 1.3 Hz, 2H), 1.82 (d, *J*= 5.9 Hz, 3H), 1.24 (td, *J*= 7.4 Hz, 1.3 Hz, 3H); ^{13}C NMR δ 190.26 (C), 140.99 (CH), 140.85 (CH), 129.84 (CH), 126.39 (CH), 23.31 (CH_2), 19.01 (CH_3), 15.03 (CH_3); MS *m/z* 156 (M^+, 15), 95 (M-SEt, 100), 67 (M-COSEt, 38); HRMS calcd. for $C_8H_{12}OS$ 156.0609, found 156.0607.

Wittig reaction of *E*-hept-2-enal (**4.20**) and S-ethyl 2-(triphenylphosphoranylidene)ethanethioate (**4.21**):
In a roundbottom flask equipped with stirring bar, triethyl phosphate S-ethyl 2-(triphenylphosphoranylidene)ethanethioate (**4.21**, 5.43 g, 14.9 mmol, 1.3 equiv) was dissolved in anhydrous CH_2Cl_2 (80 mL). The *E*-hept-2-enal (**4.20**, 1.5 mL, 11.5 mmol, 1.0 equiv) was added, the reaction mixture was heated to reflux and stirred for 20 h. The reaction mixture was then concentrated and the remaining solid was extracted with pentane (3x 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:99) yielded **4.19b** as a colorless oil.

2*E*,4*E*-S-ethylnona-2,4-dienethioate (**4.19b**):
61% yield, 14:1 *E*:*Z*-ratio, colorless oil.
^{1}H NMR δ 7.16 (dd, *J*= 15.2 Hz, 10.1 Hz, 1H), 6.22-6.09 (m, 2H), 6.05 (d, *J*= 15.2 Hz, 1H), 2.93 (q, *J*= 7.4 Hz, 2H), 2.16 (dd, *J*= 13.9 Hz, 6.7 Hz, 2H), 1.39 (dt, *J*= 14.4 Hz, 7.2 Hz, 2H), 1.34-1.29 (m, 2H), 1.26 (td, *J*= 7.4 Hz, 0.5 Hz, 3H), 0.88 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR δ 190.33 (C), 146.56 (CH), 141.14 (CH), 128.42 (CH), 126.56 (CH), 33.06 (CH_2), 30.99 (CH_2), 23.35 (CH_2), 22.44 (CH_2), 15.08 (CH_3), 14.07 (CH_3); MS *m/z* 198 (M^+, 14), 137 (M-SEt, 100), 81 (C_5H_5O, 39); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1083; *E*:*Z* ratio was determined by ^{1}H-NMR.

General procedure for the Horner-Wadsworth-Emmons reaction of an aldehyde and HWE reagent 4.23:
In a roundbottom flask equipped with stirring bar *E*-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (**4.23**, 1.5 equiv) was dissolved in anhydrous THF (20.0 mL/mmol substrate) and cooled to −78 °C. LHMDS (1 M in THF, Aldrich, 1.4 equiv) was added dropwise and the mixture stirred for 30 min. Then, the aldehyde (**4.22**, 1.0 equiv) dissolved in anhydrous THF (4.0 mL/mmol substrate) was added dropwise. After addition, the solution was allowed to warm to −40 °C (in approximately 3 h) and stirred for a total period of 16 h. A solution of aq NH_4Cl (1M, 2 mL/mmol substrate) was added and the mixture was extracted with Et_2O (3x 4 mL/mmol substrate). The combined organic extracts were dried and concentrated. Flash column chromatography (Et_2O:pentane 1:99) yielded **4.19** as a colorless oil.

2*E*,4*E*-S-ethyl 7-methylocta-2,4-dienethioate (**4.19c**):
70% yield (0.5 mmol scale), >95:5 *E*:*Z*-ratio, colorless oil.
^{1}H NMR δ 7.16 (d, *J*= 15.2 Hz, 10.0 Hz, 1H), 6.20-6.01 (m, 3H), 2.93 (q, *J*= 7.3 Hz, 2H), 2.03 (t, *J*= 6.6 Hz, 2H), 1.68 (dt, *J*= 13.3 Hz, 6.7 Hz, 1H), 1.25 (t, *J*= 7.4 Hz, 3H), 0.88 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR δ 190.29 (C), 145.28 (CH), 141.02 (CH), 129.50 (CH), 126.64 (CH), 42.65 (CH_2), 28.47 (CH), 23.33 (CH_2), 22.52 (CH_3), 15.06 (CH_2); MS *m/z* 198 (M^+, 18), 137 (M-SEt, 100); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1087; *E*:*Z* ratio was determined by ^{1}H-NMR.

2*E*,4*E*-S-ethyl 7-phenylhepta-2,4-dienethioate (**4.19d**):
39% yield (0.5 mmol scale), >95:5 *E*:*Z*-ratio, colorless oil.
^{1}H NMR δ 7.33-7.25 (m, 2H), 7.23-7.13 (m, 4H), 6.25-6.11 (m, 2H), 6.07 (d, *J*= 15.2 Hz, 1H), 2.96 (qd, *J*= 7.4 Hz, 1.1 Hz, 2H), 2.75 (t, *J*= 7.7 Hz, 2H), 2.50 (dd, *J*= 14.5 Hz, 7.0 Hz, 2H), 1.28 (td, *J*= 7.4 Hz, 1.2 Hz, 3H); ^{13}C NMR δ 190.07 (C), 144.80 (CH), 141.10 (C), 140.63 (CH), 128.92 (CH), 128.54 (CH), 128.48 (CH), 126.93 (CH), 126.20 (CH), 35.13 (CH_2), 34.96 (CH_2), 23.28 (CH_2), 14.99 (CH_3); MS *m/z* 246 (M^+, 4), 185 (M-SEt, 63), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{15}H_{18}OS$ 246.1078, found 246.1090, *E*:*Z* ratio was determined by ^{1}H-NMR.

2*E*,4*E*-S-ethyl 6-(benzyloxy)hexa-2,4-dienethioate (**4.19e**):[xii]
47% yield (0.5 mmol scale), >95:5 *E*:*Z*-ratio, colorless oil, purified by flash column chromatography (2:98 to 6:94 Et_2O:pentane).
^{1}H NMR δ 7.30-7.15 (m, 5H), 7.09 (dd, *J*= 15.2 Hz, 10.0 Hz, 1H), 6.15-6.01 (m, 2H), 5.98 (d, *J*= 15.1 Hz, 2H), 4.40 (s, 2H), 3.39 (td, *J*= 6.2 Hz, 1.5 Hz, 2H), 2.87 (qd, *J*= 7.4 Hz, 1.7 Hz, 2H), 2.24-2.16 (m, 2H), 1.72-1.61 (m, 2H), 1.19 (td, *J*= 7.4 Hz, 1.8 Hz, 3H); ^{13}C NMR δ 190.11 (C), 145.37 (CH), 140.76 (CH), 138.53 (C), 128.75 (CH), 128.49 (CH), 127.76 (CH), 127.70 (CH), 126.73 (CH), 73.05 (CH_2), 69.40 (CH_2), 29.95 (CH_2), 28.87 (CH_2), 23.27 (CH_2), 15.00 (CH_3); MS *m/z* 229 (M^+-SEt, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{17}H_{22}O_2SNa$ 313.1238, found 313.1228; *E*:*Z* ratio was determined by ^{1}H-NMR.

General procedure for the reduction of thioester to aldehyde:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, (*S*)-S-ethyl 6-(benzyloxy)-3-methylhexanethioate (**4.32**, 0.51 g, 2.21 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (5 mL). After 5 min stirring at rt the mixture was cooled to −75 °C and DIBAL-H (1.0 M solution in CH_2Cl_2, 2.66 mL, 2.66 mmol, 1.2 equiv) was added. The solution turned pink/orange. The reaction mixture was stirred for 5 h at −75 °C. Subsequently the reaction mixture was poured into a roundbottom flask with aq Rochelle's salt-solution (saturated, 10 mL), stirred for 1 h at rt and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were washed with the aq Rochelle's salt solution (2x 5 mL), dried and carefully concentrated. The aldehyde was used without further purification in the subsequent HWE reaction.

Chain extension:
4.22f and **4.39** were obtained via the general procedure for the Horner-Wadsworth-Emmons reaction of the corresponding aldehyde and HWE reagent **4.23**:

(*S*,2*E*,4*E*)-S-ethyl 10-(benzyloxy)-7-methyldeca-2,4-dienethioate (**4.22f**):[xiii, xiv]
64% yield (2 steps, 0.5 mmol scale), >95:5 *E*:*Z*-ratio, α_D^{20}= +1.2 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.30-7.17 (m, 5H), 7.12 (dd, *J*= 15.2 Hz, 9.6 Hz, 1H), 6.14-5.96 (m, 3H), 4.42 (s, 2H), 3.37 (t, *J*= 6.6 Hz, 2H), 2.88 (q, *J*= 7.4 Hz, 2H), 2.16-2.06 (m, 1H), 2.00-1.90 (m, 1H), 1.66-1.44 (m, 3H), 1.39-1.27 (m, 1H), 1.25-1.07 (m, 4H), 0.82 (d, *J*= 6.6 Hz, 3H); ^{13}C NMR δ 190.13 (C), 144.91 (CH), 140.83 (CH), 138.70 (C), 129.63 (CH), 128.47 (CH), 127.72 (CH), 127.63 (CH), 126.59 (CH), 73.02 (CH_2), 70.66 (CH_2), 40.71 (CH_2), 33.12 (CH), 33.01 (CH_2), 27.43 (CH_2), 23.27 (CH_2), 19.65 (CH_3), 15.03 (CH_3); MS *m/z* 332 (M^+, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{20}H_{28}O_2SNa$ 355.1708, found 355.1699; *E*:*Z* ratio was determined by ^{1}H-NMR.

(2*E*,4*E*,7*S*,9*S*)-S-ethyl 7,9-dimethyltrideca-2,4-dienethioate (**4.39**):
61% yield (2 steps), >95:5 *E*:*Z*-ratio, α_D^{20}= +9.4 (c= 1.0, $CHCl_3$), colorless oil.

xii The required aldehyde was prepared via known procedures. Synthesis of 4-benzyloxybutane-1-ol is described in R. P. van Summeren, D. B. Moody, B. L. Feringa, A. J. Minnaard, *J. Am. Chem. Soc.* **2006**, *128*, 4546-4547. Subsequent oxidation to the aldehyde was performed using IBX oxidation described in S. R. Harutyunyan, Z. Zhao, T. den Hartog, K. Bouwmeester, A. J. Minnaard, B. L. Feringa, F. Govers, *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 8507-8512 (4-(tert-butyldimethylsilanyloxy)but-2-enethioic acid S-ethyl ester).

xiii The required aldehyde was prepared as described in ref xii. Then subsequent Wittig olefination and asymmetric 1,4-addition were described in R. P. van Summeren, D. B. Moody, B. L. Feringa, A. J. Minnaard, *J. Am. Chem. Soc.* **2006**, *128*, 4546-4547. Finally, reduction to the aldehyde is described in ref 6f ((−)-(5*R*,7*R*,9*S*,11*S*,13*S*)-14-(*tert*-butyl-diphenyl-silanyloxy)-5,7,9,11,13-pentamethyl-tetradec-2-enethioic acid S-ethyl ester).

xiv Enantiomeric excess and regioselectivity for (*S*)-S-ethyl 6-(benzyloxy)-3-methylhexanethioate were determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99.5:0.5 heptane:*i*PrOH); retention times (min): 28.5 (*S*-enantiomer), 29.7 (*R*-enantiomer).

^{1}H NMR δ 7.19 (dd, *J*= 15.1 Hz, 9.9 Hz, 1H), 6.23-6.02 (m, 3H), 2.95 (q, *J*= 7.4 Hz, 2H), 2.23-2.14 (m, 1H), 1.96 (dt, *J*= 14.5 Hz, 7.3 Hz, 1H), 1.72-1.61 (m, 1H), 1.53-1.41 (m, 1H), 1.33-1.15 (m, 9H), 1.11-1.00 (m, 1H), 1.00-0.91 (m, 1H), 0.91-0.78 (m, 9H); ^{13}C NMR δ 190.24 (C), 145.23 (CH), 140.95 (CH), 129.60 (CH), 126.48 (CH), 44.71 (CH_2), 40.56 (CH_2), 36.59 (CH_2), 30.47 (CH), 30.12 (CH), 29.28 (CH_2), 23.28 (CH_2), 23.16 (CH_2), 20.31 (2x CH_3), 15.00 (CH_3), 14.30 (CH_3); MS *m/z* 253 (M^+-Et, 1), 109 (C_7H_9O,55), 95 (C_6H_7O, 100), 81 (C_5H_5O, 100), 55 (C_3H_3O, 74); HRMS calcd. for $C_{17}H_{31}OS$ 283.2096, found 283.2090.

General procedure for the enantioselective 1,6-conjugate addition:[7, xv]
(exemplified for the addition of MeMgBr to **4.22b**)
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuBr•SMe_2 (5.14 mg, 25 µmol, 5.0 mol%) and (*S,R*)-reversed Josiphos (15.46 mg, 26 µmol, 5.25 mol%) were dissolved in anhydrous CH_2Cl_2 (2 mL). After 5 min stirring at rt the mixture was cooled to −70 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 0.33 mL, 1.0 mmol, 2.0 equiv) was added. After stirring for an additional 10 min, a solution of **4.22b** (70.1 mg, 0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (additional 0.5 mL) was added with a syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at −70 °C and subsequently EtOH (0.1 mL) and an aq NH_4Cl-solution (1 M, 0.5 mL) were added. The mixture was warmed to rt and an additional 5 mL of the NH_4Cl-solution and 5 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:99) yielded **4.33b** as a colorless[xvi] oil.

(*S,E*)-S-ethyl 5-methylnon-3-enethioate (**4.33b**):
83% yield, 89% ee, 99:1 regioselectivity (1,6:1,4), α_D^{20}= +9.0 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 5.50-5.39 (m, 2H), 3.19 (d, *J*= 5.7 Hz, 2H), 2.84 (q, *J*= 7.4 Hz, 2H), 2.18-2.04 (m, 1H), 1.31-1.16 (m, 9H), 0.96 (d, *J*= 6.7 Hz, 3H), 0.86 (t, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.74 (C), 142.55 (CH), 119.57 (CH), 47.89 (CH_2), 36.94 (CH), 36.73 (CH_2), 29.70 (CH_2), 23.50 (CH_2), 22.98 (CH_2), 20.55 (CH_3), 14.90 (CH_3), 14.33 (CH_3); MS *m/z* 214 (M^+, 10), 124 (M-SEt-Et, 34), 83 (C_6H_{11}, 46), 69 (C_5H_9, 100); HRMS calcd. for $C_{12}H_{22}OS$ 214.1391, found 214.1401.
Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 98°C in 4.8 min, 98 °C for 200 min; retention times (min): 163.8 (an enantiomer of the 1,4-addition product), 191.1 (*R*-enantiomer), 192.3 (*S*-enantiomer).

(*S,E*)-S-ethyl 5,7-dimethyloct-3-enethioate (**4.33c**):
84% yield, 82% ee, 95:5 regioselectivity (1,6:1,4), α_D^{20}= +8.3 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 5.51-5.37 (m, 2H), 3.18 (d, *J*= 5.6 Hz, 2H), 2.84 (q, *J*= 7.4 Hz, 2H), 2.26-2.14 (m, 1H), 1.63-1.50 (m, 1H), 1.32-1.11 (m, 5H), 0.94 (d, *J*= 6.7 Hz, 3H), 0.83 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR δ 198.69 (C), 142.58 (CH), 119.48 (CH), 47.87 (CH_2), 46.45 (CH_2), 34.77 (CH), 25.63 (CH), 23.50 (CH_2), 23.21 (CH_3), 22.56 (CH_3), 20.93 (CH_3), 14.92 (CH_3); MS *m/z* 214 (M^+,1), 89 (C_3H_5OS, 24), 83 (C_6H_{11}, 29), 69 (C_4H_5O, 100), 55 (C_3H_3O, 32); HRMS calcd. for $C_{12}H_{22}OSNa$ 237.1289, found 237.1280.
Enantiomeric excess was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 80 °C in 3 min, 80 °C for 40 min, 80 °C to 160 °C in 8 min, 160 °C for 4 min; for 2,4-dimethylpentanoic acid;[xvii] retention times (min): 53.7 (*S*-enantiomer), 54.0 (*R*-enantiomer). Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

[xv] This reaction has been performed up to 2.7 mmol scale. For reactions at larger scale extended reaction time are required. Typically >95% conversion was achieved in up to 40 h.
[xvi] Occasionally the product was polluted with a yellow coloured side product undetectable by GC/MS or NMR.
[xvii] 2,4-dimethylpentanoic acid was obtained by Ru-catalyzed $NaIO_4$-oxidation as described in P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936-3938.

(*S*,*E*)-S-ethyl 5-methyl-7-phenylhept-3-enethioate (**4.33d**):
78% yield, 82% ee, 99:1 regioselectivity (1,6:1,4), α_D^{20}= +4.1 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.33-7.16 (m, 5H), 5.62-5.46 (m, 2H), 3.26 (d, *J*= 5.5 Hz, 2H), 2.90 (q, *J*= 7.4 Hz, 2H), 2.75-2.51 (m, 2H), 2.28-2.15 (m, 1H), 1.72-1.60 (m, 2H), 1.27 (t, *J*= 7.4 Hz, 3H), 1.07 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.22 (C), 142.69 (C), 141.78 (CH), 128.50 (CH), 128.36 (CH), 125.72 (CH), 120.35 (CH), 47.74 (CH_2), 38.68 (CH_2), 36.50 (CH), 33.69 (CH_2), 23.41 (CH_2), 20.57 (CH_3), 14.85 (CH_3); MS *m/z* 262 (M^+,1), 200 (M^+-SEtH, 16), 131 ($C_{10}H_{11}$, 40), 117 (C_5H_9OS, 15), 104 (C_4H_8OS, 20), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{16}H_{24}OS$ 263.1470, found 263.1464.
Enantiomeric excess and regioselectivity were determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99:1 heptane:*i*PrOH); retention times (min): 14.7 (1,4-addition product), 19.6 (*S*-enantiomer), 17.9 (*R*-enantiomer).

(*S*,*E*)-S-ethyl 8-(benzyloxy)-5-methyloct-3-enethioate (**4.33e**):
This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O: pentane).
86% yield, 86% ee, 94:6 regioselectivity (1,6:1,4), α_D^{20}= +5.9 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.36-7.24 (m, 5H), 5.54-5.41 (m, 2H), 4.49 (s, 2H), 3.45 (t, *J*= 6.6 Hz, 2H), 3.20 (dd, *J*= 3.9 Hz, 1.6 Hz, 2H), 2.85 (q, *J*= 7.4 Hz, 2H), 2.20-2.09 (m, 1H), 1.70-1.52 (m, 2H), 1.45-1.30 (m, 2H), 1.23 (t, *J*= 7.4 Hz, 3H), 1.00 (d, *J*= 6.7 Hz, 3H).; ^{13}C NMR δ 198.37 (C), 141.91 (CH), 138.78 (C), 128.45 (CH), 127.71 (CH), 127.58 (CH), 119.97 (CH), 72.95 (CH_2), 70.57 (CH_2), 47.73 (CH_2), 36.80 (CH), 33.34 (CH_2), 27.66 (CH_2), 23.42 (CH_2), 20.51 (CH_3), 14.85 (CH_3); MS *m/z* 277 (M^+-Et, 1), 153 ($C_9H_{13}O_2$, 14), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{18}H_{26}O_2SNa$ 329.1551, found 329.1538.
Enantiomeric excess was determined by chiral HPLC analysis, column: Chiralcel-OJ-H, (98:2 heptane:*i*PrOH); for *E*-methyl 8-(benzyloxy)-5-methyloct-3-enoate;[xviii] retention times (min): 23.5 (*S*-enantiomer), 24.7 (*R*-enantiomer). Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

***Syn*-selective enantioselective 1,6-addition:**
(5*S*,7*S*,*E*)-S-ethyl 10-(benzyloxy)-5,7-dimethyldec-3-enethioate (**4.33f**):
88% yield, 87% *syn*-product (**4.33f**) and 13% of *anti*-product (**4.33g**), 85:15 regioselectivity (1,6:1,4), α_D^{20}= −0.9 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.38-7.23 (m, 5H), 5.52-5.25 (m, 2H), 4.50 (s, 2H), 3.44 (t, *J*= 6.7 Hz, 2H), 3.19 (d, *J*= 6.4 Hz, 2H), 2.86 (q, *J*= 7.4 Hz, 2H), 2.32-2.19 (m, 1H), 1.72-1.01 (m, 10H), 1.00-0.92 (m, 3H), 0.89-0.79 (m, 3H); residual absorptions 1,4-addition product: 2.75-2.64 (m, 1H), 2.50 (ddd, *J*= 36.1 Hz, 14.4 Hz, 7.3 Hz, 2H), residual absorptions α,β-unsaturated 1,6-addition product: 2.04-1.76 (m, 1H); ^{13}C NMR δ 198.55 (C), 142.21 (CH), 138.81 (C), 128.47 (CH), 127.73 (CH), 127.59 (CH), 119.73 (CH), 72.99 (CH_2), 70.96 (CH_2), 47.76 (CH_2) , 44.51 (CH_2), 34.59 (CH), 33.93 (CH_2), 30.25 (CH), 27.34 (CH_2), 23.40 (CH_2), 21.43 (CH_3), 19.50 (CH_3), 14.93 (CH_3); residual absorptions *anti*-product: 198.68 (C), 142.71 (CH), 119.28 (CH), 44.37 (CH_2), 34.31 (CH), 33.22 (CH_2), 30.16 (CH), 20.30 (CH_3), 19.91 (CH_3), 14.83 (CH_3); residual absorptions 1,4-addition product of the 1,6-ACA: 135.20, 128.16, 54.33, 51.35, 44.88, 42.91, 39.91, 33.09, 32.92, 21.71, 20.41; MS *m/z* 319 (M^+-Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{21}H_{32}O_2SNa$ 371.2021, found 371.2010.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time. Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

[xviii] *E*-methyl 8-(benzyloxy)-5-methyloct-3-enoate was obtained via the following procedure; The substrate (~10 mg) was dissolved in MeOH (0.5 mL) and stirred for 3 h in the presence of K_2CO_3 (excess). Then an aq NH_4Cl-solution (1M, 0.5 mL) was added and the layers were separated. After extraction with Et_2O (2x 0.5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Filtration over a short SiO_2-column (eluent Et_2O) and evaporation of the solvent yielded the product as a colorless oil.

(5*S*,7*S*,9*S*,*E*)-S-ethyl 5,7,9-trimethyltridec-3-enethioate (**4.40**):
87% yield, 91% *syn*-product (**4.40**) and 9% of *anti*-product (**4.41**), 90:10 regioselectivity (1,6:1,4), α_D^{20}= −2.4 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 5.53-5.25 (m, 2H), 3.20 (d, *J*= 6.6 Hz, 2H), 2.90-2.81 (m, 2H), 2.26 (dt, *J*= 13.6 Hz, 6.7 Hz, 14H), 1.61-1.39 (m, 3H), 1.34-1.10 (m, 10H), 1.06-0.74 (m, 14H). residual absorptions 1,4-addition product of the 1,6-ACA: 2.69 (dd, *J*= 13.9 Hz, 7.0 Hz, 1H), 2.50 (ddd, *J*= 38.1 Hz, 14.4 Hz, 7.3 Hz, 2H). residual absorptions α,β-unsaturated 1,6-ACA product: 1.97 (dd, *J*= 12.7 Hz, 7.0 Hz, 2H), 1.79-1.69 (m, 2H); ^{13}C NMR δ 198.59 (C), 142.32 (CH), 119.76 (CH), 47.80 (CH_2), 45.82 (CH_2), 44.54 (CH_2), 36.76 (CH_2), 34.63 (CH), 30.00 (CH), 29.35 (CH_2), 27.72 (CH_2), 23.42 (CH), 23.20 (CH_2), 21.64 (CH_3), 20.33 (2x CH_3), 14.84 (CH_3), 14.34 (CH_3); residual absorptions 1,4-addition product of the 1,6-ACA: 51.40, 39.66, 30.49; MS *m/z* 269 (M^+-Et, 1), 111 ($C_7H_{11}O$, 57), 97 (C_6H_9O,55), 69 (C_4H_5O, 100), 57 (C_4H_9, 75), 55 (C_3H_3O, 62); HRMS calcd. for $C_{18}H_{34}OSNa$ 321.2228, found 321.2217.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time. Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

***Anti*-selective enantioselective 1,6-addition:**
(5*R*,7*S*,*E*)-S-ethyl 10-(benzyloxy)-5,7-dimethyldec-3-enethioate (**4.33g**):
83% yield, 78% *anti*-product (**4.33g**) and 22% of *syn*-product (**4.33f**), 87:13 regioselectivity (1,6:1,4), α_D^{20}= −2.2 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.38-7.24 (m, 5H), 5.53-5.25 (m, 2H), 4.51 (s, 2H), 3.50-3.40 (m, 2H), 3.24-3.15 (m, 2H), 2.86 (qd, *J*= 7.4 Hz, 1.4 Hz, 2H), 2.32-2.19 (m, 4H), 1.74-1.09 (m, 10H), 0.96 (dd, *J*= 9.0 Hz, 6.7 Hz, 3H), 0.90-0.77 (m, 3H); residual absorptions 1,4-addition product of the 1,6-ACA: 2.70 (dd, *J*= 13.8 Hz, 6.7 Hz, 1H), 2.50 (ddd, *J*= 35.0 Hz, 14.3 Hz, 7.2 Hz, 2H); residual absorptions α,β-unsaturated 1,6-ACA product: 2.05-1.95 (m, 1H), 1.86-1.75 (m, 1H), 1.02 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.55 (C), 142.72 (CH), 138.81 (C), 128.46 (CH), 127.73 (CH), 127.59 (CH), 119.28 (CH), 72.99 (CH_2), 71.01 (CH_2), 47.77 (CH_2), 44.37 (CH_2), 34.31 (CH), 33.23 (CH_2), 30.17 (CH), 27.24 (CH_2), 23.42 (CH_2), 20.31 (CH_3), 19.91 (CH_3), 14.83 (CH_3); residual absorptions *syn*-product: 142.22 (CH), 119.73 (CH), 44.51 (CH_2), 34.59 (CH), 33.93 (CH_2), 30.25 (CH), 27.35 (CH_2), 21.44 (CH_3), 19.51 (CH_3), 14.93 (CH_3); residual absorptions 1,4-addition product of the 1,6-ACA: 135.18, 128.27, 51.37, 39.96, 33.05, 32.97, 27.45, 20.45; MS *m/z* 319 (M^+-Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{21}H_{32}O_2SNa$ 371.2021, found 371.2010.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time. Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

(5*R*,7*S*,9*S*,*E*)-S-ethyl 5,7,9-trimethyltridec-3-enethioate (**4.41**):
85% yield, 72% *anti*-product (**4.41**) and 28% of *syn*-product (**4.40**), 90:10 regioselectivity (1,6:1,4), α_D^{20}= +2.5 (c= 1.0, CH_2Cl_2), colorless oil.
^{1}H NMR δ 5.54-5.24 (m, 2H), 3.23-3.11 (m, 2H), 2.92-2.77 (m, 2H), 2.33-2.17 (m, 1H), 1.59-1.38 (m, 3H), 1.33-1.12 (m, 10H), 1.08-0.64 (m, 14H); residual absorptions 1,4-addition product of the 1,6-ACA: 2.77-2.64 (m, 1H), 2.50 (ddd, *J*= 37.7 Hz, 14.4 Hz, 7.3 Hz, 1H) ; residual absorptions α,β-unsaturated 1,6-ACA product: 2.03-1.93 (m, 1H), 1.78-1.67 (m, 1H); ^{13}C NMR δ 198.72 (C), 142.95 (CH), 119.13 (CH), 47.81 (CH_2), 45.48 (CH_2), 44.56 (CH_2), 36.51 (CH_2), 34.26 (CH), 30.07 (CH), 29.31 (CH_2), 27.68 (CH_2), 23.43 (CH), 23.21 (CH_2), 20.60 (CH_3), 20.50 (CH_3), 20.46 (CH_3), 20.10 (CH_3), 14.34 (CH_3); residual absorptions *syn*-product: 198.55 (C), 142.32 (CH), 119.76 (CH), 45.82 (CH_2), 44.70 (CH_2), 36.75 (CH_2), 34.63 (CH), 30.45 (CH), 21.64 (CH_3), 20.33 (CH_3), 14.84 (CH_3); residual absorptions 1,4-addition product of the 1,6-ACA: 135.09, 128.40, 51.41, 39.80, 36.70, 34.51, 20.16, 14.93; MS *m/z* 269 (M^+-Et, 1), 111 ($C_7H_{11}O$, 57), 97 (C_6H_9O,55), 69 (C_4H_5O, 100), 57 (C_4H_9, 75), 55 (C_3H_3O, 62); HRMS calcd. for $C_{18}H_{35}OS$ 299.2403, found 299.2404.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time. Regioselectivity was determined by ^{1}H-NMR with 10 sec d1-time.

General procedure for the isomerization of the β,γ-unsaturated thioester to the α,β-unsaturated thioester: [xix]

(exemplified for the isomerization of **4.33b**)

In a dried roundbottom flask equipped with cooler and stirring bar under a N_2 atmosphere, **4.33b** (0.37 g, 1.7 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (18 mL). After 5 min stirring at rt DBU (1.3 mL, 8.6 mmol, 5.0 equiv) was added and the reaction mixture immediately turned yellow/orange. The reaction mixture was heated to reflux and stirred for 16 h. Subsequently an aq NH_4Cl-solution (1M, 20 mL) and 10 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 10 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:99) yielded **4.35b** as a colorless oil.

(*S*,*E*)-S-ethyl 5-methylnon-2-enethioate (**4.35b**) data in accordance with data described in ref 4d.

91% yield of a mixture of 88% α,β-, 12% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, α_D^{20}= +1.0 (c= 1.0, $CHCl_3$), literature value:[4d] α_D= −2.0 (c= 1.0, $CHCl_3$) for *S*-enantiomer, colorless oil.

The ratio of α,β- and β,γ-products was determined by ^{1}H NMR with 10 sec d1-time.

(*S*,*E*)-S-ethyl 5,7-dimethyloct-2-enethioate (**4.35c**):

87% yield of a mixture of 90% α,β-, 10% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, α_D^{20}= −4.3 (c= 1.0, $CHCl_3$), colorless oil.

^{1}H NMR δ 6.86 (dt, *J*= 15.2 Hz, 7.5 Hz, 1H), 6.08 (dt, *J*= 15.4 Hz, 1.4 Hz, 1H), 2.93 (q, *J*= 7.4 Hz, 2H), 2.24-2.11 (m, 1H), 2.05-1.92 (m, 1H), 1.77-1.51 (m, 2H), 1.33-0.77 (m, 14H); residual absorptions β,γ-unsaturated 1,6-ACA product and 1,4-addition product of the 1,6-ACA: 5.49-5.23 (m), 3.19 (d), 2.89-2.80 (m), 2.74-2.65 (m), 2.53 (dd), 2.48-2.41 (m), 1.84 (t); ^{13}C NMR δ 190.14 (C), 144.34 (CH), 129.90 (CH), 46.37 (CH_2), 40.07 (CH_2), 30.31 (CH), 25.34 (CH), 23.37 (CH_3), 23.16 (CH_2), 22.27 (CH_3), 19.77 (CH_3), 14.95 (CH_3); residual absorptions β,γ-unsaturated 1,6-ACA product and 1,4-addition side product from 1,6-ACA: 142.47, 134.92, 128.62, 119.40, 51.38, 47.78, 41.94, 34.68, 34.51, 28.48, 25.54, 22.47, 22.36, 22.32, 20.84, 20.46; MS *m/z* 214 (M^+,1), 153 (M^+-SEt, 46), 83 (C_6H_{11}, 39), 55 (C_3H_3O, 64); HRMS calcd. for $C_{12}H_{22}OSNa$ 237.1289, found 237.1279.

The ratio of α,β- and β,γ-products was determined by ^{1}H NMR with 10 sec d1-time.

(*S*,*E*)-S-ethyl 5-methyl-7-phenylhept-2-enethioate (**4.35d**):

This reaction was performed at rt. Reaction at reflux gave lower yield and contamination with a side product.

87% yield of a mixture of 89% α,β-, 11% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, 80 % ee, α_D^{20}= +3.9 (c= 1.0, $CHCl_3$), colorless oil.

^{1}H NMR δ 7.33-7.22 (m, 2H), 7.21-7.12 (m, 3H), 6.86 (dt, *J*= 15.3 Hz, 7.5 Hz, 1H), 6.09 (d, *J*= 15.5 Hz, 1H), 2.94 (q, *J*= 7.4 Hz, 2H), 2.79-2.46 (m, 2H), 2.30-2.00 (m, 2H), 1.76-1.59 (m, 2H), 1.55-1.41 (m, 1H), 1.28 (td, *J*= 7.4 Hz, 1.8 Hz, 3H), 0.97 (d, *J*= 6.5 Hz, 3H); ^{13}C NMR δ 190.05 (C), 143.85 (CH), 142.44 (C), 130.03 (CH), 128.46 (CH), 128.42 (CH), 125.85 (CH), 39.63 (CH_2), 38.56 (CH_2), 33.48 (CH_2), 32.27 (CH_2), 23.16 (CH), 19.61 (CH_3), 14.93 (CH_3); MS *m/z* 262 (M^+,1), 105 (C_8H_9, 17), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{16}H_{23}OS$ 263.1470, found 263.1464.

Enantiomeric excess was determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99:1 heptane:*i*PrOH); retention times (min): 16.6 (*S*-enantiomer β,γ-unsaturated 1,6-ACA product), 17.8 (*R*-enantiomer β,γ-unsaturated 1,6-ACA product), 19.9 (*S*-enantiomer α,β-unsaturated 1,6-ACA product), 24.8 (*R*-enantiomer α,β-unsaturated 1,6-ACA product).

The ratio of α,β- and β,γ-products was determined by ^{1}H NMR with 10 sec d1-time.

[xix] This reaction was performed from 0.3 mmol up to 1.7 mmol scale.

(*S*,*E*)-S-ethyl 8-(benzyloxy)-5-methyloct-2-enethioate (**4.35e**):
This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O: pentane).
86% yield of a mixture of 89% α,β-, 11% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, α_D^{20}= −1.6 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.35-7.19 (m, 5H), 6.82 (dt, *J*= 15.3 Hz, 7.5 Hz, 1H), 6.05 (d, *J*= 15.5 Hz, 1H), 4.45 (s, 2H), 3.41 (t, *J*= 6.6 Hz, 3H), 2.90 (q, *J*= 7.4 Hz, 2H), 2.20-2.10 (m, 1H), 2.04-1.94 (m, 1H), 1.68-1.48 (m, 2H), 1.43-1.29 (m, 2H), 1.27-1.20 (m, 3H), 0.87 (d, *J*= 6.7 Hz, 3H); residual absorptions β,γ-unsaturated 1,6-ACA product: 5.46-5.41 (m, 2H), 3.16 (d, *J*= 5.6 Hz, 3H), 2.81 (q, *J*= 7.4 Hz, 2H) 1.20-1.15 (m, 3H), 0.96 (dd, *J*= 6.7 Hz, 3.5 Hz, 3H); ^{13}C NMR δ 190.01 (C), 144.01 (CH), 138.63 (C), 129.93 (CH), 128.42 (CH), 127.69 (CH), 127.57 (CH), 72.98 (CH_2), 70.52 (CH_2), 39.64 (CH_2), 33.14 (CH), 32.56 (CH_2), 27.36 (CH_2), 23.11 (CH_2), 19.61 (CH_3), 14.91 (CH_3); residual absorptions β,γ-unsaturated 1,6-ACA product: 141.86 (CH), 119.91 (CH), 69.66 (CH_2), 51.23 (CH_2), 47.68 (CH_2), 36.75 (CH), 33.29 (CH_2), 27.60 (CH_2), 20.45 (CH_3); MS *m/z* 277 (M^+-Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{18}H_{26}O_2SNa$ 329.1551, found 329.1540.
The ratio of α,β- and β,γ-products was determined by ^{1}H NMR with 10 sec d1-time.

General procedure for the enantioselective 1,4-conjugate addition:[4d, xx]
(exemplified for the addition of MeMgBr to **4.35b**)
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the previously prepared Josiphos-complex[4d] (5.54 mg, 7.5 μmol, 1.0 mol%) was dissolved in anhydrous *t*BuOMe (3.05 mL). After 5 min stirring at rt the mixture was cooled to −78 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 0.38 mL, 1.1 mmol, 1.5 equiv) was added. After stirring for an additional 10 min, a solution of **4.35b** (0.16 mg, 0.75 mmol, 1.0 equiv) in anhydrous *t*BuOMe (additional 0.75 mL) was added via a syringe pump over a period of 0.5 h. The reaction mixture was stirred overnight (16 h including addition) at −78 °C and subsequently EtOH (0.1 mL) and an aq NH_4Cl-solution (1M, 0.5 mL) were added. The mixture was warmed to rt and an additional 5 mL of the aq NH_4Cl-solution and 5 mL of Et_2O were added and the layers were separated. After extraction with Et_2O (2x 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:99) yielded **4.36b** as a colorless oil.

(3*S*,5*S*)-S-ethyl 3,5-dimethylnonanethioate data in accordance with data described in ref 4d.
83% yield of a mixture of 96% *syn*-product (**4.36b**) and 4% of *anti*-product (**4.37b**), 92% ee, α_D^{20}= −1.3 (c= 1.0, $CHCl_3$), literature value:[4d] α_D= +2.3 (c= 0.5, $CHCl_3$) for (*R*,*R*)-enantiomer, colorless oil.
Ratio *syn*- and *anti*-product and enantiomeric excess were determined by chiral GC analysis as described previously in ref 4d, column: Chiralsil-Dex-CB, 50 °C to 80°C in 3 min, 80 °C for 90 min, 80 °C to 140°C in 60 min, retention times (min): 140.2 ((3*S*,5*S*)-enantiomer), 142.1 ((3*S*,5*R*)-enantiomer), 142.5 ((3*R*,5*S*)-enantiomer).

(3*R*,5*S*)-S-ethyl 3,5-dimethylnonanethioate data in accordance with data described in ref 4d.
77% yield of a mixture of 92% *anti*-product (**4.37b**) and 8% of *syn*-product (**4.36b**), 85% ee, α_D^{20}= +13.9 (c= 1.0, $CHCl_3$), literature value:[4d] α_D= −8.9 (c= 0.5, $CHCl_3$) for (3*S*,5*R*)-enantiomer, colorless oil.
Ratio *syn*- and *anti*-product and enantiomeric excess were determined by chiral GC analysis as described previously in ref 4d, column: Chiralsil-Dex-CB, 50 °C to 80°C in 3 min, 80 °C for 90 min, 80 °C to 140°C in 60 min, retention times (min): 140.3 ((3*S*,5*S*)-enantiomer), 140.9 ((3*R*,5*R*)-enantiomer), 142.1 ((3*S*,5*R*)-enantiomer), 142.5 ((3*R*,5*S*))-enantiomer).

[xx] This reaction was performed from 0.3 mmol up to 5.0 mmol scale.

(3*S*,5*S*)-S-ethyl 3,5,7-trimethyloctanethioate (**4.36c**):
67% yield of a mixture of 90% *syn*-**4.36c** and 10% of *anti*-**4.37c**, α_D^{20}= −9.1 (c= 1.0, CH_2Cl_2), colorless oil.
^{1}H NMR δ 2.87 (q, *J*= 7.4 Hz, 2H), 2.53 (dd, *J*= 14.3 Hz, 5.3 Hz, 1H), 2.28 (dd, *J*= 14.3 Hz, 8.5 Hz, 1H), 2.18-2.07 (m, 1H), 1.70-1.47 (m, 2H), 1.29-1.17 (m, 4H), 1.14-1.06 (m, 1H), 1.05-0.79 (m, 14H); ^{13}C NMR δ 199.51 (C), 51.44 (CH_2), 46.59 (CH_2), 45.24 (CH_2), 28.71 (CH), 27.75 (CH), 25.29 (CH), 23.79 (CH_3), 23.43 (CH_2), 22.17 (CH_3), 20.31 (CH_3), 20.28 (CH_3), 14.98 (CH_3); residual absorptions *anti*-product: 47.49, 44.60, 30.47, 22.52, 19.38; MS *m/z* 201 (M^+-Et, 4), 112 (M^+-SEt-$(CH_3)_2CHCH_2$, 31), 95 (C_6H_7O, 95), 69 (C_4H_5O, 100), 57 (C_4H_9, 55), 55 (C_3H_3O, 37); HRMS calcd. for $C_{13}H_{27}OS$ 231.1777, found 231.1777.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time.

(3*S*,5*S*)-S-ethyl 3,5-dimethyl-7-phenylheptanethioate (**4.36d**):
73% yield of a mixture of 94% *syn*-**4.36d** and 6% of *anti*-**4.37d**, α_D^{20}= −4.8 (c= 1.0, $CHCl_3$), colorless oil.
^{1}H NMR δ 7.42-7.34 (m, 2H), 7.33-7.24 (m, 3H), 2.98 (q, *J*= 7.4 Hz, 2H), 2.83-2.73 (m, 1H), 2.72-2.58 (m, 2H), 2.40 (dd, *J*= 14.4 Hz, 8.3 Hz, 1H), 2.30-2.17 (m, 1H), 1.81-1.59 (m, 2H), 1.58-1.47 (m, 1H), 1.47-1.39 (m, 1H), 1.35 (t, *J*= 7.4 Hz, 3H), 1.15 (ddd, *J*= 11.6 Hz, 10.2 Hz, 7.0 Hz, 1H), 1.06 (d, *J*= 6.5 Hz, 3H), 1.02 (d, *J*= 6.6 Hz, 3H); residual absorptions *anti*-product: 2.56 (1H), 2.47 (dd, *J*= 14.4 Hz, 7.8 Hz, 1H); ^{13}C NMR δ 199.37 (C), 143.00 (C), 128.40 (2x CH), 125.70 (CH), 51.38 (CH_2), 44.44 (CH_2), 38.55 (CH_2), 33.28 (CH_2), 29.83 (CH), 28.75 (CH), 23.41 (CH_2), 20.23 (CH_3), 20.11 (CH_3), 14.96 (CH_3); residual absorptions *anti*-product: 44.12 (CH_2), 19.38 (CH_3); MS *m/z* 217 (M^+-SEt, 13), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{17}H_{27}OS$ 279.1783, found 279.1777.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time.

(3*S*,5*S*)-S-ethyl 8-(benzyloxy)-3,5-dimethyloctanethioate (**4.36e**):
This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O:pentane).
64% yield of a mixture of 94% *syn*-**4.36e** and 6% of *anti*-**4.37e**, α_D^{20}= −2.8 (c= 1.0, CH_2Cl_2), colorless oil.
^{1}H NMR δ 7.38-7.24 (m, 5H), 4.51 (d, *J*= 2.1 Hz, 2H), 3.45 (td, *J*= 6.7 Hz, 2.3 Hz, 2H), 2.87 (qd, *J*= 7.4 Hz, 2.5 Hz, 2H), 2.52 (ddd, *J*= 14.4 Hz, 5.3 Hz, 2.3 Hz, 1H), 2.28 (ddd, *J*= 14.4 Hz, 8.5 Hz, 2.5 Hz, 1H), 2.18-2.06 (m, 1H), 1.73-1.63 (m, 1H), 1.63-1.53 (m, 1H), 1.53-1.44 (m, 1H), 1.44-1.34 (m, 1H), 1.31-1.19 (m, 4H), 1.19-1.08 (m, 1H), 1.08-0.98 (m, 1H), 0.93 (dd, *J*= 6.6 Hz, 2.4 Hz, 3H), 0.89 (dd, *J*= 6.5 Hz, 2.4 Hz, 3H); ^{13}C NMR δ 199.37 (C), 138.77 (C), 128.44 (CH), 127.75 (CH), 127.58 (CH), 73.00 (CH_2), 70.87 (CH_2), 51.33 (CH_2), 44.58 (CH_2), 33.08 (CH_2), 30.02 (CH), 28.74 (CH), 27.20 (CH_2), 23.39 (CH_2), 20.31 (CH_3), 20.06 (CH_3), 14.95 (CH_3); MS *m/z* 322 (M^+, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{19}H_{30}O_2S$ 323.2039, found 323.2036.
The ratio of *syn*- and *anti*-products was determined by ^{13}C NMR with 10 sec d1-time.

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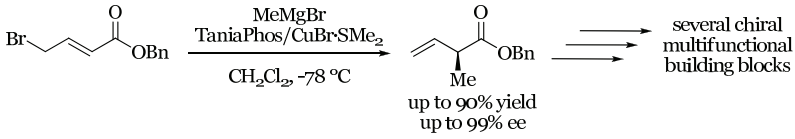
Chapter 5

Cu-Catalyzed Asymmetric Allylic Alkylation of 4-Halocrotonates: Efficient Synthesis of Versatile Multifunctional Building Blocks

In this chapter the highly enantioselective synthesis of α-Me substituted esters in up to 90% yield and up to 99% ee via Cu-catalyzed allylic alkylation is described. The transformation proved scalable to at least 6.6 mmol (1.7 g). The selective synthesis of α-alkyl substituted esters via allylic alkylation with other, more reactive, alkyl Grignard reagents was unsuccessful. To illustrate the versatility of the α-Me substituted esters, the allylic alkylation products have been elaborated to multifunctional building blocks with a single or with multiple stereogenic centers.



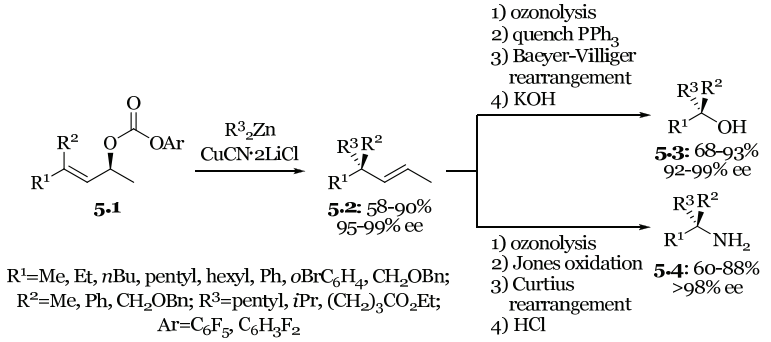
Parts of this chapter have been published in:
(a) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824-2852. (b) T. den Hartog, B. Maciá, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Cat.* **2010**, *352*, 999-1013.

5.1 Synthesis of small chiral multifunctional building blocks and natural products via asymmetric allylic alkylation

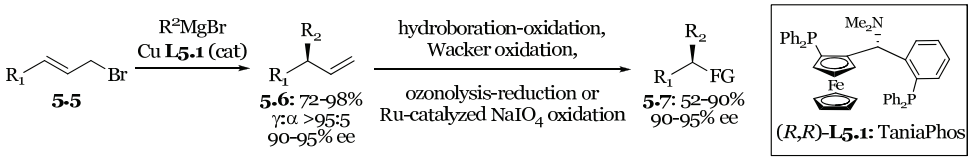
Small, enantiopure multifunctional building blocks are frequently selected as the starting materials of choice in retrosynthetic analyses of complex natural products.[1] Cu-catalyzed asymmetric allylic alkylation (AAA)[2] is one of the emerging methodologies for the enantioselective formation of C-C bonds and has been used to prepare several of these building blocks.[3]

For example, Knochel and co-workers[3a] elaborated the products obtained from their diastereoselective allylic alkylation with zinc reagents[4] to desirable tertiary amines and alcohols in high yields and with minimal loss of stereochemical integrity (Scheme 5.1). Furthermore, our group[3b] recently reported routes to a variety of bifunctional building blocks, elaborated from the product of the Cu-TaniaPhos (**L5.1**)-catalyzed enantioselective allylic alkylation of functionalized allylic bromides with Grignard reagents[3b,5] (Scheme 5.2). Finally, Breit and co-workers[3c] prepared natural occurring deoxypropionate and propionate substructures from intermediates synthesized via their *syn*-diastereoselective allylic alkylation with Grignard reagents[6] (Scheme 5.3).

Scheme 5.1. *Synthesis of chiral tertiary alcohols and amines from allylic alkylation products.*[3a]

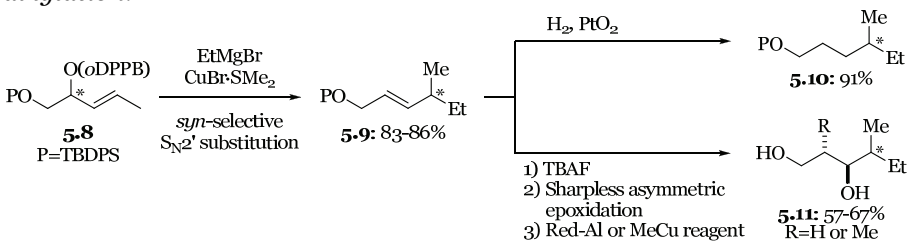


Scheme 5.2. *Elaboration of allylic alkylation products to optically active bifunctional building blocks.*[3b]



Used abbreviation: FG=functional group.

Scheme 5.3. *Synthesis of deoxypropionate and propionate units via allylic alkylation.*[3c]

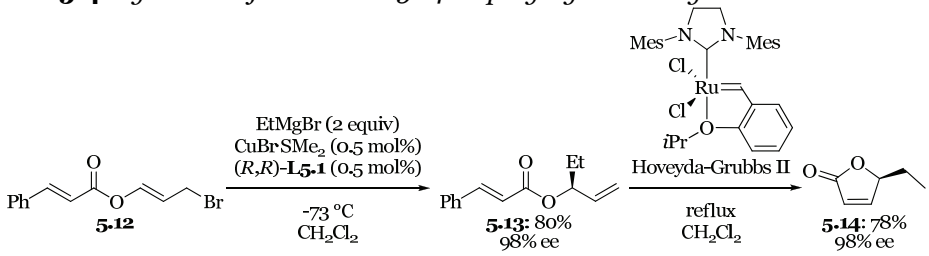


Used abbreviation: P=protective group, *o*DPPB=*ortho* diphenylphosphanyl benzoate.

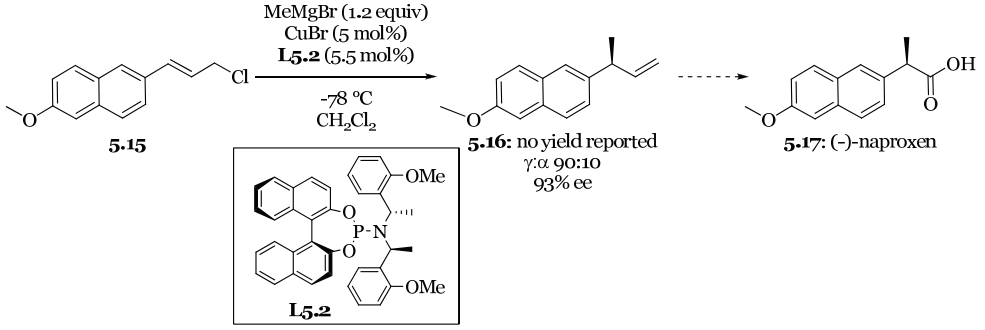
In addition to the synthesis of multifunctional chiral building blocks, the AAA with Grignard reagents has been used as key step in the preparation of several natural products. For example, in 2006 our group reported[5c] a straightforward synthesis of the naturally occurring butenolide (*S*)-5-ethyl-2(5H)-furanone (**5.14**) via a simple catalyzed route based on the *h*-AAA reaction and subsequent ring closing metathesis (Scheme 5.4). Submission of the allylic bromide **5.12** to standard *h*-AAA conditions provided intermediate **5.13** in good yield and excellent enantioselectivity. Subsequent ring closing metathesis of **5.13**, without loss of integrity of the stereogenic center, gave butenolide **5.14**.

Furthermore, Alexakis and co-workers described[7] a formal synthesis of (–)-naproxen (**5.17**, Scheme 5.5), the enantiomer of the non-steroidal anti-inflammatory drug, based on their Cu-phosphoramidite catalyzed AAA method.[8] The intermediate **5.16** was obtained from the naphthyl substrate **5.15** with good regioselectivity and excellent enantioselectivity. Oxidation of the double bond to the acid would yield (–)-naproxen **5.17** via a short and convenient route.

Scheme 5.4. *Synthesis of butenolide 5.14 employing Cu-catalyzed h-AAA.*



Scheme 5.5. *Formal synthesis of (–)-naproxen.*

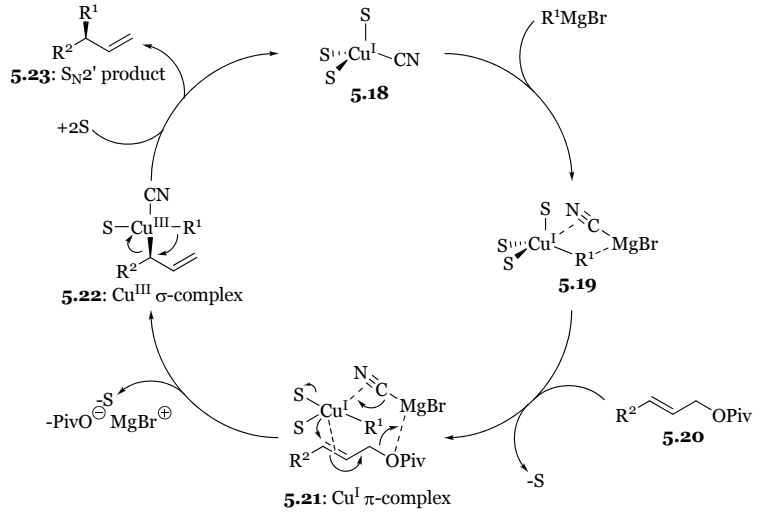


5.2 An introduction to the mechanism of the AAA with Grignard reagents

In spite of the substantial amount of literature on the Cu-catalyzed AAA (see paragraph 1.10), no studies on the mechanism of the Cu-catalyzed AAA are known. The difficulties associated with the low temperatures employed and the high turnover frequencies encountered are presumably the main reasons for the hiatus in our understanding of the mechanism for the AAA.

In 1986 Goering and coworkers[9] proposed the catalytic cycle depicted in Figure 5.1 for the S_N2'-selective substitution of allylic pivalates with alkyl Grignard reagents catalyzed by 1 to 3 mol% of CuCN. In the proposed mechanism[10] initially the catalyst **5.18** and the Grignard reagent combine to form copper-Grignard complex **5.19**. Intermediate **5.19** then forms a Cu^I π-complex[11] (**5.21**) with substrate **5.20**. For **5.21** the copper coordinates to the olefin and, possibly, the Lewis acidic magnesium coordinates to the leaving group. From complex **5.21**, oxidative addition and allylic rearrangement gives Cu^{III} σ-complex **5.22**. Subsequently, reductive elimination from **5.22** gives the S_N2' product **5.23** and reforms the catalyst **5.18**.

Figure 5.1. *Proposed mechanism by Goering and co-workers for Cu-catalyzed allylic alkylation.*

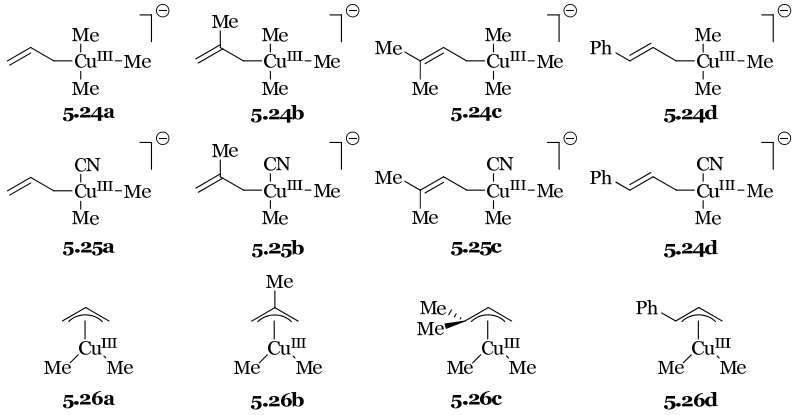


Used abbreviations: S=solvent (in this case Et_2O).
Please note that: 1) The number of coordinating solvent molecules was not specified in the proposed mechanism. In this figure the coordination of solvent molecules results in 18 electron Cu^I- and 16 electron Cu^{III}-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules.

This proposed mechanism, published 24 years ago,[9] is still the working model for the allylic alkylation with Grignard reagents. One of the structures in the proposed mechanism, the d8 Cu^{III} σ-complex **5.22**, has been under heavy debate for those two decades. Only recently[12] Bertz and co-workers[13] succeeded to observe several

d8 Cu^{III} σ-complexes (**5.24a** to **5.24d** and **5.25a** to **5.25d**) in solution using rapid injection NMR spectroscopy at −100 °C (Figure 5.2). Complexes **5.24a** to **5.24d** were formed from the reaction of two equiv of Me_2CuLi•LiI with either allylic chlorides or allylic acetates; while the reaction of Me_2CuLi•LiCN with allylic chlorides or allylic acetates gave products **5.25a** to **5.25d**.

Figure 5.2. *Cu^{III} intermediates observed by rapid injection NMR spectroscopy.*



In analogy with the proposed mechanism by Goering and co-workers,[9] the catalytic cycle depicted in Figure 5.3 (next page) can be proposed for the mechanism of the AAA with Grignard reagents catalyzed by Cu-TaniaPhos (**L5.1**, Scheme 5.2).[14] In the mechanism the monomeric precatalyst[i] **5.27** and a Grignard reagent form the active catalyst **5.28**.[ii] Interaction with substrate **5.29** then forms the Cu^{I} π-complex **5.30**. Subsequently, oxidative insertion and allylic rearrangement from **5.30** gives the d8 Cu^{III} σ-complex **5.31**. Finally, reductive elimination forms the S_N2'-product (**5.23**) and reforms the active catalyst complex **5.28** by interaction with another Grignard reagent.

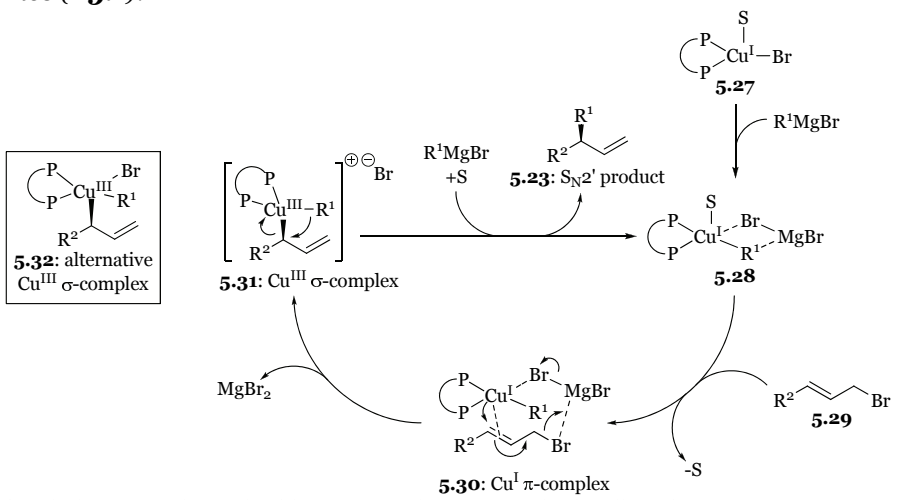
The structure for **5.31** is debatable since all known stable Cu^{III}-species have been found to be 16 electron structures with a square planar geometry. As the depicted 16 electron Cu^{III}-species, **5.31** is charged and adopts a distorted square planar geometry to facilitate interaction with the TaniaPhos ligand.[iii] Presumably, this complex has a bromide as counterion. Alternatively, **5.31** can be envisioned to be an 18 electron 5-coordinated Cu^{III}-species in a square pyramidal geometry with the bromide directly coordinated to the copper (**5.32**). Further research should provide more information on this complex.

[i] In contrast to the dimeric JosiPhos-Cu complex (see paragraph 3.2) the TaniaPhos-Cu complex is monomeric. An agostic interaction with the hydrogen adjacent to the NMe_2 group might be the main reason that the Cu-TaniaPhos complex is monomeric (unpublished results).

[ii] In analogy to the mechanism of the asymmetric conjugate addition (see paragraph 3.2) $MgBr_2$ is still present in this complex.

[iii] The bite angle for the TaniaPhos on copper in the crystal structure of **5.27** is 115° (unpublished results).

Figure 5.3. *Tentative catalytic cycle for the AAA with Grignard reagents catalyzed by TaniaPhos (**L5.1**).*

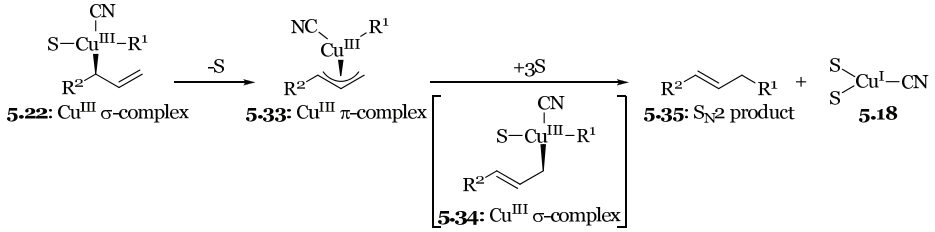


Used abbreviations: S=solvent (in this case CH_2Cl_2). P-P=TaniaPhos ligand.
Please note that: 1) The number of coordinating solvent molecules results in 18 electron Cu^I-species. 2) The Grignard reagent is drawn as a monomeric species for clarity. In reality the Grignard reagent is either an aggregate or coordinated to one or more solvent molecules. 3) *Trans* or *cis* relationship with respect to the distinct phosphor atoms of TaniaPhos are not taken into account in the depiction of this mechanism.

The typical competing reaction for AAA is S_N2-substitution. Goering and co-workers[9] proposed the pathway depicted in Figure 5.4 for the formation of the S_N2 side-product. From the Cu^{III} σ-complex **5.22** (the precursor for the reductive elimination forming the S_N2'-product in Figure 5.1), via isomerization, the Cu^{III} η^3 π-allyl complex **5.33** is formed. Then reductive elimination from **5.33** gives both the S_N2 product **5.35** and reforms the catalyst (**5.18**).

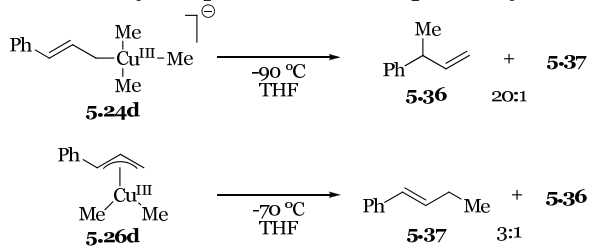
In 1984, Goering and co-workers[9] proposed that Cu^{III} σ-complex **5.34** (Figure 5.4) is formed, before reductive elimination can take place. However, recent calculations by Nakamura and co-workers[15] have shown that reductive elimination will proceed directly from intermediate **5.34**, via an enyl [σ+π]-type structure.[15] In the same study Nakamura and co-workers[15] calculated that the formation of S_N2-product (i.e. **5.35**) is favored starting from Cu^{III} π-complex **5.33** over the formation of S_N2'-product (i.e. **5.23**). This computational result supports the pathway proposed in Figure 5.4 for the formation of S_N2-product.

Figure 5.4. *The formation of S_N2 side-product from intermediate **5.22**.*



Please note that the amount of coordinating solvent molecules was not specified in the proposed mechanism. In this figure the number of coordinating solvent molecules results in 18 electron Cu^I-species.

Scheme 5.6. *The formation of S_N2 product and S_N2' product from Cu^{III} intermediates.*



Similar to the controversy on the existence of the Cu^{III} σ-intermediate, the formation of Cu^{III} π-allyl intermediate **5.33** has been under debate for over two decades and only recently Bertz and co-workers[13] could directly observe several η³ Cu^{III} π-allyl intermediates (**5.26a** to **5.26d**) by rapid injection NMR spectroscopy. The Cu^{III} π-allyl intermediates **5.26a** to **5.26d** were formed from the corresponding Cu^{III} σ-intermediates **5.24a** to **5.24d** over time.[13] In support of the mechanism proposed by Goering and co-workers,[9] from intermediate **5.24d** mainly S_N2' product (Scheme 5.6, **5.36**, at −90 °C) is formed,[iv] while the S_N2 product (**5.37**, at −70 °C) is the main product from the reductive elimination of intermediate **5.26d**.

To summarize the preceding, from the Cu^{III} σ-intermediate (i.e. **5.22**) either by reductive elimination the S_N2' product is formed, or by isomerization a Cu^{III} π-allyl intermediate (i.e. **5.33**) is formed. The latter ultimately leads to the S_N2-product. Thus, the rate of reductive elimination vs. the rate of isomerization determines the ratio between S_N2 and S_N2' product.

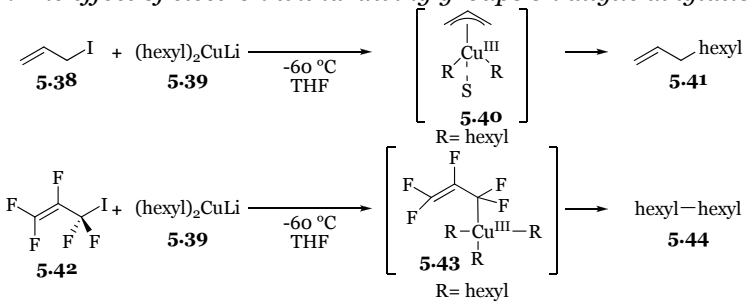
Several factors influence the ratio of S_N2 and S_N2' product. First of all, Goering and co-workers[9] found a large influence of the counterion on the S_N2':S_N2-ratio. Using copper with the good π-acceptor ligand CN, mainly S_N2' product was obtained. On the contrary, for copper in combination with poor π-acceptor ligands, like halogens or SCN, mainly S_N2 product was obtained. Interestingly, in the rapid injection NMR study by Bertz and co-workers[13] no conversion of **5.24a** to **5.26a** (Figure 5.2) was observed in the presence of the strongly σ-donating, weakly π-accepting, ligand P(*n*Bu)$_3$ and only slow conversion of **5.25a** to **5.26a** was observed, presumably due to the π-accepting CN group.

Temperature has a big influence on the ratio of S_N2' and S_N2 products also, as can be seen from faster conversion of **5.25a** to **5.26a** at higher temperatures in the rapid injection NMR study by Bertz and co-workers.[13]

Finally, electronics should play an important role in determining the S_N2':S_N2-ratio. In calculations by Nakamura, Bäckvall and co-workers[16] a distinct difference between the reactivity of allyl iodide and pentafluoroallyl iodide was

[iv] The studies in ref 13 indicate that the Cu^{III}-intermediates **5.22** and **5.31** might be preceded by initial coordination of the Cu-catalyst to the terminal C. Alternatively, the Cu^{III}-intermediates **5.22** and **5.31**possibly have to be replaced by intermediates for which the Cu-catalyst is coordinated to the terminal C-atom instead of the internal C-atom. However, further studies are needed to determine the correct representation of these intermediates since these intermediates are most likely strongly dependant on the ligand on Cu and the counterion.

Scheme 5.7. *The effect of electron withdrawing groups on allylic alkylations.*



shown (Scheme 5.7). For the reaction of allyl iodide (**5.38**) with $(hexyl)_2CuLi$ (**5.39**) the product is the cross-coupling product **5.41**; while for the reaction of pentafluoroallyl iodide (**5.42**) with $(hexyl)_2CuLi$ (**5.39**) the product is the homocoupling product dodecane **5.44**. Calculations show that the intermediate pentafluoroallyl species **5.43**, formed from pentafluoroallyl iodide, acts as an η^1-spectator ligand on the Cu^{III} intermediate; while the allyl species **5.40**, from allyl iodide, acts as an η^3-actor ligand. Furthermore, calculations show that the electron poor pentafluoroallyl species preferentially forms Cu^{III} σ-complex **5.43**, while the allyl species forms a Cu^{III} π-complex **5.40**. This computational result suggests that (more) electron poor allyl species are less likely to form Cu^{III} π-complexes.

Unfortunately, in the reports on AAA few examples are known for which the electronic properties of the substrates can be compared (Table 5.1 and Table 5.2). For the Cu-catalyzed AAA employing TaniaPhos[17] (**L5.1**) as ligand, the difference between S_N2:S_N2' ratio of cinnamyl bromide (Table 5.1, entry 1) and the slightly more inductive electron withdrawing *para* chlorocinnamyl bromide (entry 2) is negligible. For the Cu-catalyzed AAA of 2-substituted allylic chlorides with phosphoramidite ligands,[18] the ratios of S_N2:S_N2' product for the cinnamyl chloride (Table 5.2, entry 1) and *para* chlorocinnamyl chloride (entry 2) are again similar. For the mild electron donating *para* methyl substituted allylic chloride (entry 3) more S_N2 product is obtained.[19] Finally, the difference in S_N2' vs. S_N2 ratio between aryl substituted (Table 5.1, entry 1, 2) and linear alkyl substituted (entry 3) allylic bromides is substantial. Electronic effects, either inductive or via resonance, can be the main reason for this effect. However, the effect of forming an extended π-system including the phenyl moiety, favoring the Cu^{III} π-allyl complex, cannot be ruled out.

A final factor[v] influencing the S_N2':S_N2-ratio is sterics. For example, for the sterically encumbered *t*Bu substituted allylic bromide[20] (Table 5.1, entry 4) the formation of S_N2 product is favored over the S_N2' product.[vi]

To conclude, in this paragraph a tentative mechanistic cycle for the Cu-TaniaPhos catalyzed AAA, as well as, a pathway for the formation of the

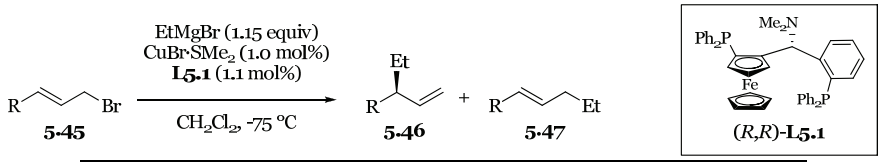
[v] Apparently there is also an influence of the Grignard reagent on the S_N2:S_N2'-ratio. Goering and co-workers[9] found formation of a 1:1 mixture of S_N2 and S_N2' product for allylic alkylation using either PhMgBr or propen-2-yl-MgBr. The substrate in this example was symmetric (with exception of a D-label) so presumably both products are formed via a Cu^{III} π-allyl intermediate. A good explanation for the ready formation of the π-allyl intermediate is still lacking. However, probably the different properties of the sp^2 hybridized C-atoms, i.e. electronic properties and geometry, might account for this effect.

[vi] See also paragraph 5.10.

S_N2 side-product are proposed. However, further research is required to validate these proposals. Especially in view of the fact that the collected data presented here are obtained using a variation in important parameters (i.e. different solvents, leaving groups, addition modes and temperatures).

Two immediate investigations required to obtain more insight in the mechanism of the AAA are a thorough study of the kinetics of the AAA and the influence of electron withdrawing and donating groups on both the S_N2':S_N2 ratio and on the kinetics of the AAA.

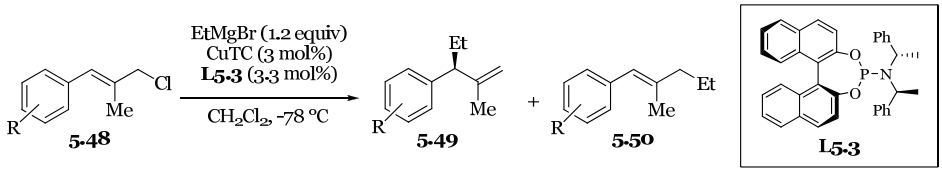
Table 5.1. *Cu-catalyzed AAA with the ligand TaniaPhos.*



entry	R^1	yield (%)	S_N2': S_N2	ee (%)
1	Ph	92	81:19	95
2	*p*ClC_6H_4	80	82:18	96
3	*n*Bu	99[a]	100:0	93
4	*t*Bu	20[a]	25:75	22

[a] Conversion.

Table 5.2. *Cu-catalyzed AAA with a phosphoramidite ligand.*

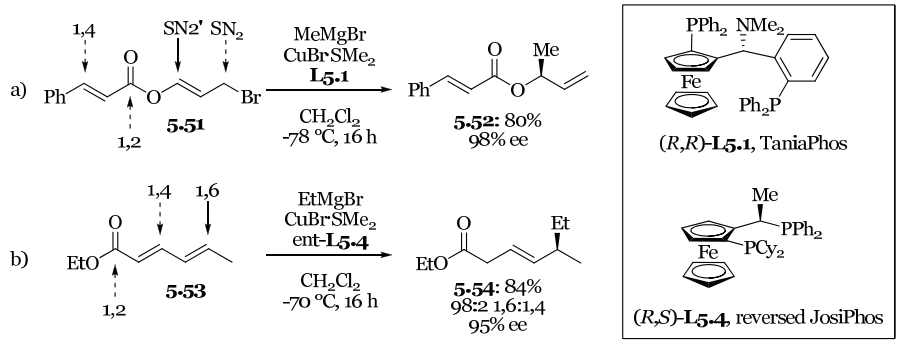


entry	R	yield (%)	S_N2': S_N2	ee (%)
1	*p*Cl	87	92:8	96
2	H	87	92:8	98
3	*p*Me	85	84:16	96

5.3 Selective functionalization of substrates with multiple reactive sites

In the ongoing research to broaden the scope of the Cu-catalyzed AAA[3b,5] and asymmetric conjugate addition (ACA)[21] with Grignard reagents, our group has recently focused our attention towards novel substrates with multiple reactive sites. Recent examples of chemo-, regio- and enantioselective reactions of this type are the hetero-AAA[5c] (Scheme 5.8a, next page) and the asymmetric 1,6-addition[22] (Scheme 5.8b). In the hetero-AAA, using Cu-catalysis employing TaniaPhos (**L5.1**), S_N2' addition is favored over 1,4-addition, 1,2-addition and S_N2 addition.[5c] In the asymmetric 1,6-addition (see chapters 2 to 4), the use of Cu-catalysis employing reversed JosiPhos (**L5.4**), favors addition to the δ-position (1,6-addition) over addition to either the β-position (1,4-addition) or addition to the ester functionality (1,2-addition).[22]

Scheme 5.8. *Asymmetric Cu-catalyzed hetero-AAA (a) and 1,6-addition (b).*



Other substrates with chemo-, regio-, and stereoselectivity issues are 4-halocrotonates (Figure 5.5). For these substrates organometallic reagents can attack on every carbon-atom. Our current challenge is to selectively achieve asymmetric Cu-catalyzed S_N2'-addition with reactive Grignard reagents.

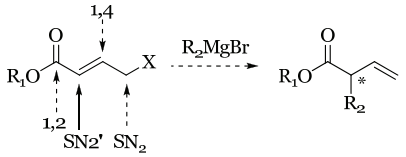


Figure 5.5. *Desired allylic alkylation of 4-halocrotonates with Grignard reagents.* X=halogen.

5.4 Asymmetric allylic alkylation of 4-halocrotonates

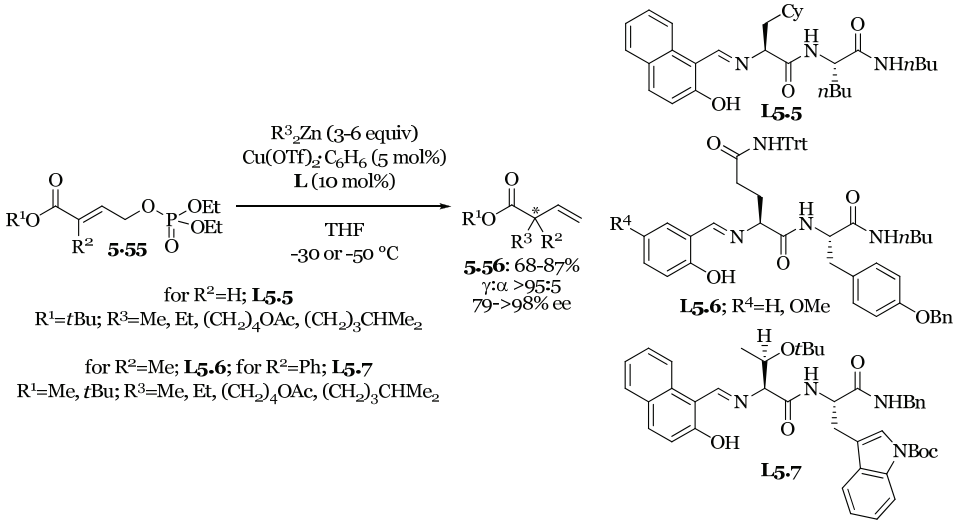
The use of crotonates with a leaving group in the 4-position for allylic alkylation was pioneered by Hoveyda and co-workers.[23] Using a combination of $(CuOTf)_2 \cdot C_6H_6$ and chiral peptidic Schiff base ligands for the AAA of a variety of dialkylzinc reagents, tertiary[23a] and quaternary carbon-centers[23b] were constructed with high regioselectivity and ee (Scheme 5.9). This methodology requires the use of 6 equiv of Me_2Zn for the construction of the prominent Me-substituted tertiary carbon-centers[24] with high ee (90%).[23a] Recently, 4-halocrotonates were transformed in the Cu-free AAA[23c] with selected Grignard reagents using *N*-heterocyclic carbene ligands in up to excellent ee (Scheme 5.10).

Although α-alkyl substituted acids, amides and esters are abundant in nature, the building blocks prepared via AAA have, so far, only seen limited use in natural product synthesis.[23a,25] This lack of application might be due to the stereogenic center α to the ester moiety which is prone to epimerization.

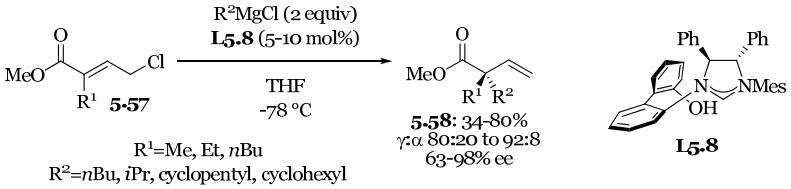
In this chapter we describe the highly selective AAA of the non-toxic MeMgBr (only 1.2 equiv required) to 4-bromocrotonates using Cu-catalysis with the commercially available TaniaPhos (**L5.1**). Furthermore, we describe the elaboration of the allylic alkylation products to a variety of versatile acyclic and cyclic multifunctional building blocks with a single or with multiple stereogenic centers.

The described transformations illustrate that, with optimized methods, the sensitive α-Me substituted β,γ-unsaturated esters can be successfully elaborated and thus represent a highly versatile addition to current chiral building blocks and our repertoire for the preparation of natural products.

Scheme 5.9. *Asymmetric allylic alkylation with dialkylzinc reagents of crotonates with a leaving group in the 4-position.*



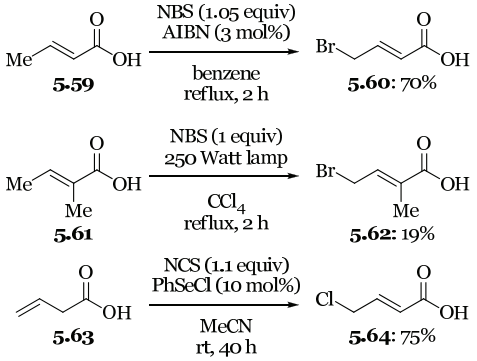
Scheme 5.10. *Cu-free allylic alkylation of 4-halocrotonates with selected Grignard reagents.*



5.5 Synthesis of 4-halocrotonates

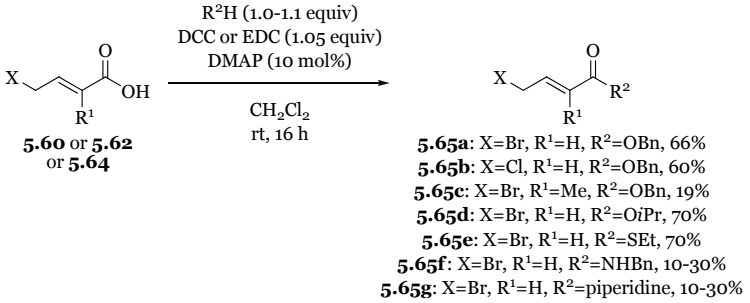
The synthesis of 4-halocrotonic esters, thioesters and amides started with the synthesis of 4-halocrotonic acids (Scheme 5.11, next page). Using crotonic acid (**5.59**) or tiglic acid (**5.61**) the corresponding 4-bromo α,β-unsaturated acids (**5.60** and **5.62**[26]) were obtained via radical bromination in low to good yields. The low yield for 4-bromo tiglic acid (**5.62**) is explained by the difficult separation of the desired product and the other regioisomer of the bromination, 2-(bromomethyl)but-2-enoic acid. Finally, chlorocrotonic acid (**5.64**) was obtained in good yield using a Se-catalyzed halogenation[27] with vinylacetic acid (**5.63**) as substrate.

Scheme 5.11. *Synthesis of 4-halocrotonic acids.*



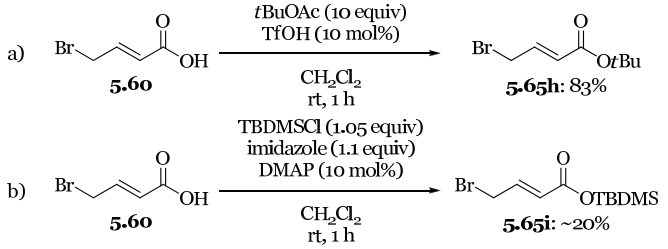
Several ester, thioester and amide substrates for the AAA were subsequently obtained by carbodiimide mediated coupling of the corresponding carboxylic acids with alcohols, thiols and amines in good yields (Scheme 5.12).

Scheme 5.12. *Synthesis of ester, thioester and amide substrates for AAA.*



Two more ester substrates were obtained via other routes. *E-tert* butyl 4-bromobut-2-enoate (**5.65h**, Scheme 5.13a) was obtained in good yield from bromocrotonic acid (**5.60**) via an acid catalyzed transesterification with *tert* butyl acetate, while *E-tert* butyldimethylsilyl 4-bromobut-2-enoate (**5.65i**, Scheme 5.13b) was obtained via coupling of TBDMSCl and bromocrotonic acid (**5.60**) in low yield

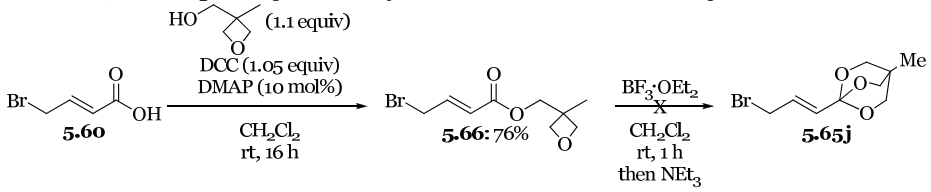
Scheme 5.13. *Synthesis of two ester substrates for AAA.*



with 33% impurity of a silyl containing side-product.[vii]

Finally, attempts to obtain orthoester **5.65 j** were unsuccessful (Scheme 5.14). The Lewis acid mediated rearrangement of ester **5.66**, obtained via DCC coupling,[viii] gave a complex mixture of products, also after column chromatography.

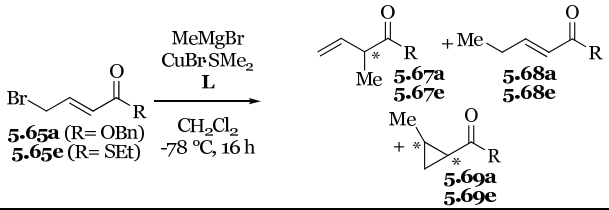
Scheme 5.14. *Attempted synthesis of 4-bromo orthoester **5.65 j**.*



5.6 AAA of 4-halocrotonates with MeMgBr

We initially chose the Br-substituted α,β-unsaturated ester **5.65a** (Table 5.3) as substrate[ix] and focused on a regioselective addition of MeMgBr (Table 5.3). Using non-ligated CuBr•SMe_2 at −40 °C or employing either reversed JosiPhos (**L5.4**, Figure 5.6, next page) or JosiPhos (**L5.9**) at −78 °C in CH_2Cl_2, a mixture of S_N2- (**5.67a**) and S_N2'-products (**5.68a**) was obtained (entry 1 to 3). However, the use of TaniaPhos (**L5.1**) gave selectively the S_N2'-product (**5.67a**, entry 4). When the more reactive Michael acceptor **5.65e** was used in combination with **L5.1**, a mixture of α-substituted alkyl thioester **5.67e** and cyclopropane **5.69e** was found. The formation of the latter product is attributed to a tandem 1,4-addition-intramolecular enolate trapping (see further chapter 6).[28]

Table 5.3. *Ligand screening for regioselective S_N2'-alkylation using MeMgBr.*[a]



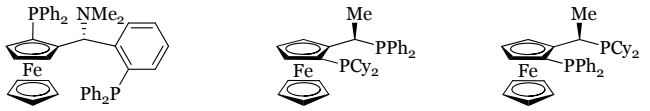
entry	substrate	R	ligand	conversion[b]	**5.67**[b]	**5.68**[b]	**5.69**[b]
1	**5.65a**	OBn	none[c]	full	50%	50%	-
2	**5.65a**	OBn	**L5.4**[d]	93%	52%	27%	-
3	**5.65a**	OBn	**L5.5**[d]	76%[e]	31%	26%	-
4	**5.65a**	OBn	**L5.1**	full	>95%	<5%	-
5	**5.65**[e]	SEt	**L5.1**[f]	full	49%	-	47%

[a] Conditions: **5.65a** or **5.65e** in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O, 1.2 equiv), ligand (1.1 mol%) and CuBr•SMe_2 (1 mol%) in CH_2Cl_2 (0.2 M in **5.65**). [b] Conversion and % **5.67**, **5.68**, and **5.69** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [c] CuBr•SMe_2 (1 equiv) was used at −40 °C. [d] **L** (2.2 mol%) and CuBr•SMe_2 (2 mol%) were used. [e] 19% of benzyl crotonate obtained (see paragraph 5.8). [f] **L5.1** (5.5 mol%) and CuBr•SMe_2 (5 mol%) were used.

[vii] Possibly the side-product is an alternative conformer of the ester observed exclusively by ^{1}H-NMR spectroscopy.

[viii] The use of EDC for this coupling gave a complex mixture of products.

[ix] This substrate was chosen mainly due to its physical properties (i.e. UV-activity and low volatility).

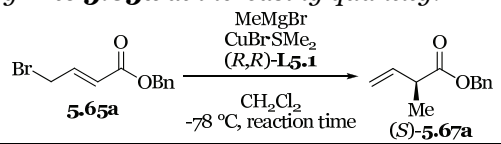


(*R*,*R*)-**L5.1**, TaniaPhos (*R*,*S*)-**L5.4**, reversed JosiPhos (*R*,*S*)-**L5.9**, JosiPhos

Figure 5.6. *Chiral ferrocenyl-based phosphines used in AAA and ACA of Grignard Reagents.*
Used abbreviation: Cy=cyclohexyl.

The addition of MeMgBr to **5.65a** using only 1 mol% Cu-TaniaPhos catalyst at 0.5 mmol scale provides product **5.67a** (Table 5.4, entry 1) in excellent yield (86%) and ee (99%). This is the highest ee so far for the introduction of a Me-group *via* AAA. Furthermore, only traces (<5%) of the S_N2-product were observed. Performing the reaction in up to 6.6 mmol (1.7 g) scale[x] gave the product again in excellent yields and enantioselectivities, albeit with somewhat longer reaction times (entries 2 to 5). As expected, using (*S*,*S*)-TaniaPhos for the transformation led to the opposite enantiomer of the product with high ee (entry 2).[xi]

Table 5.4. *AAA of MeMgBr to* ***5.65a*** *at increasing quantity.*[a]



entry	scale	reaction time	yield	ee[b]
1	0.5 mmol, 0.12 g	2 h	86%	99%
2[c]	2.0 mmol, 0.51 g	40 h	81%[d]	96%[d]
3	2.5 mmol, 0.64 g	16 h	88%	98%
4	4.0 mmol, 1.02 g	16 h	87%	98%
5	6.6 mmol, 1.68 g	16 h	90%	98%

[a] Conditions: **5.65a** (1 equiv) in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O, 1.2 equiv), (*R*,*R*)-**L5.1** (1.1 mol%) and CuBr•SMe_2 (1 mol%) in CH_2Cl_2 (0.2 M in **5.65a**). [b] Determined by chiral HPLC. [c] (*S*,*S*)-**L5.1** was used and (*R*)-**5.67a** was obtained. [d] See footnote xi.

5.7 AAA of 4-halocrotonates with alkyl Grignard reagents

In contrast to the highly selective AAA of **5.65a** with MeMgBr, the reaction of **5.65a** with more reactive alkyl Grignard reagents proceeds with low selectivity. Apparently, **5.65a** is a quite reactive substrate since the blank reaction, omitting any copper catalyst, already gives full conversion in 16 h to a mixture of mainly S_N2 and 1,4-addition products (Table 5.5, entry 1). However, the high reactivity of the substrate towards EtMgBr also leads to low reproducibility as can be seen from

[x] The reaction has been performed at 10 mmol scale as well and gave 88% yield and 96% ee. By improving the experimental conditions (presumably longer addition of the substrate to the reaction mixture is required) a higher ee might be obtained.

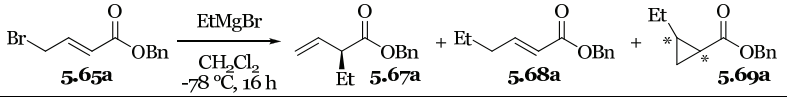
[xi] Apparently, allowing the reaction to proceed for 40 h gives slightly lower yield. The slightly lower ee might be explained by analysis issues due to overlapping of the large first peak and small second peak for this enantiomer on the chiral HPLC.

the inconsistent results of the addition of either EtMgBr to **5.65a** in CH_2Cl_2 (entry 2 and 3) or diluted **5.65a** to EtMgBr in CH_2Cl_2 (entry 4 and 5). From the experiments described in Table 5.5 the conclusion can be drawn that only traces of an S_N2'-product are formed from a blank reaction.

To improve the selectivity towards the S_N2'-product, the use of Cu-catalysis was explored (Table 5.6, next page). Using a stoichiometric amount of ligand-free CuBr•SMe_2 gave a slight improvement towards the selectivity for the S_N2'-product (**5.67a**, entry 1). The use of catalytic amounts of CuBr•SMe_2 in combination with TaniaPhos (**L5.1**) gave further improvement of selectivity towards γ-substitution (entry 2 and 3). In addition to S_N2'-product **5.67a** also substantial amounts of benzyl crotonate (**5.70**), as well as S_N2 (**5.68a**) and 1,4-addition products (**5.69a** and **5.71a**) were found. Benzyl crotonate (**5.70**) is presumably formed by transmetalation and subsequent quenching during work-up (see further paragraph 5.8). The formation of benzyl crotonate (**5.70**) could be suppressed using a reversed addition protocol; that is the slow addition of EtMgBr to a solution of catalyst and substrate **5.65a** in CH_2Cl_2 (entry 4). The slow addition of the Grignard reagent also improved the selectivity towards γ-substitution. However, addition of the Grignard over an extended amount of time (entry 5, 5 h addition) did not lead to further improvement of the selectivity towards the S_N2'-product (**5.67a**). A variety of other ligands were screened (entry 6 to 9) and gave either benzyl crotonate (**5.70**, entry 6, JosiPhos (**L5.9**)), S_N2 product (**5.68a**, entry 7 and 8, reversed Josiphos (**L5.4**) and phosphoramidite ligand **L5.3**, respectively) or 1,4-addition product (**5.69a**, entry 9, Tol-BINAP (**L5.10**)) as main product.

Since TaniaPhos (**L5.1**) gave the most encouraging results regarding the S_N2':S_N2 ratio, several solvents were screened for the Cu-TaniaPhos catalyzed AAA with EtMgBr (Table 5.7). The use of *t*BuOMe as solvent gave low conversion and precipitation during the reaction (entry 2). When toluene was used for the reaction the main product was benzyl crotonate (**5.70**, entry 3). So, CH_2Cl_2 was chosen as optimal solvent for further studies.

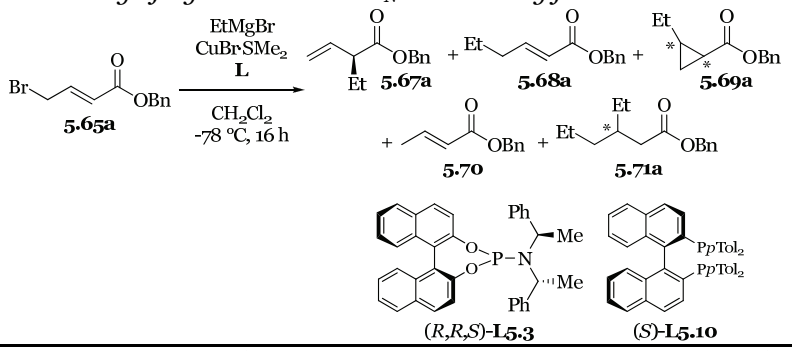
Table 5.5. *Blank reaction of EtMgBr with* ***5.65a***.[a,b]



entry	addition mode	S_N2': **5.67a**[c]	S_N2: **5.68a**[c]	1,4-addition: **5.69a**[c]
1	Grignard reagent	2%	82%	16%
2[d]	Grignard reagent	4%	35%	47%
3	Grignard reagent	-	31%	69%
4[e]	substrate	-	22%	61%
5	substrate	-	52%	48%

[a] Conditions: EtMgBr (3.0 M in Et_2O, 1.5 equiv) was added to a solution of **5.65a** in CH_2Cl_2; or **5.65a** in CH_2Cl_2 was added to a solution of EtMgBr in CH_2Cl_2. [b] In all cases the starting material was completely consumed. [c] % **5.67a**, **5.68a** and **5.69a** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [d] In addition to the products in the table 7% benzyl crotonate and 7% double addition product (subsequent S_N2 and 1,4-addition) were obtained. [e] In addition to the products in the table 8% benzyl crotonate and 9% double addition product were obtained.

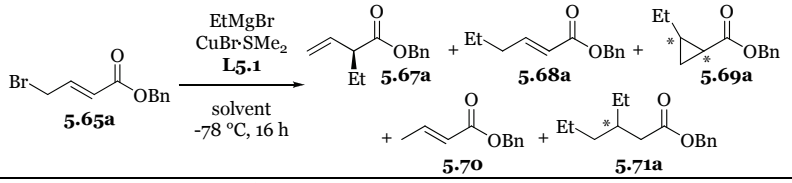
Table 5.6. *Screening of ligands towards S_N2'-selectivity for the AAA with EtMgBr.*[a,b]



entry	ligand	S_N2': **5.67a**[c]	S_N2: **5.68a**[c]	1,4-: **5.69a**[c]	**5.70**[c]	S_N2 and 1,4-: **5.71a**[c]
1	none[d]	11%	40%	-	24%	26%
2	**L5.1**	16%	28%	12%	38%	6%
3	**L5.1**[e]	22%	35%	8%	30%	-
4[f]	**L5.1**	28%	27%	39%	<5%	-
5[g]	**L5.1**[e]	18%	34%	20%	15%	8%
6	**L5.5**	11%	37%	-	52%	-
7	**L5.9**	15%	72%	-	14%	-
8	**L5.3**[e,h]	11%	77%	-	-	11%
9	**L5.10**[h]	-	-	48%	18%	34%

[a] Conditions: **5.65a** in CH_2Cl_2 was added dropwise to a solution of EtMgBr (3.0 M in Et_2O, 1.2 equiv), ligand (1.1 mol%) and CuBr•SMe_2 (1 mol%) in CH_2Cl_2 (0.2 M in **5.65a**). [b] In all cases the starting material was completely consumed. [c] % **5.67a**, **5.68a**, **5.69a**, **5.70** and **5.71a** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [d] 1 equiv CuBr•SMe_2 was used and the reaction was performed at −40 °C. [e] Ligand (5.25 mol%) and CuBr•SMe_2 (5 mol%) were used. [f] Dropwise addition of EtMgBr. [g] Slow addition of EtMgBr in 5 h. [h] CuI was used as copper source.

Table 5.7. *Screening of solvents for the Cu-TaniaPhos catalyzed AAA with EtMgBr.*[a]

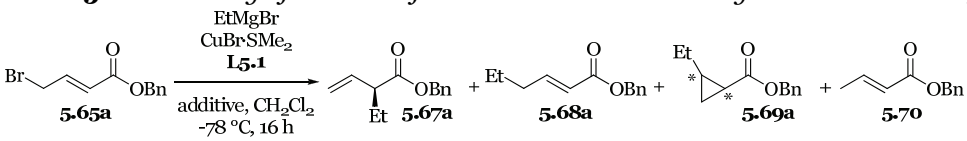


entry	ligand	S_N2': **5.67a**[b]	S_N2: **5.68a**[b]	1,4-: **5.69a**[b]	**5.70**[b]	S_N2 and 1,4-: **5.71a**[b]
1	CH_2Cl_2[c]	11%	40%	-	24%	26%
2	*t*BuOMe[d]	-	7%	-	25%	-
3	toluene[c]	7%	24%	8%	50%	5%

[a] Conditions: **5.65a** in solvent was added dropwise to a solution of EtMgBr (3.0 M in Et_2O, 1.2 equiv), ligand (1.1 mol%) and CuBr•SMe_2 (1 mol%) in solvent (0.2 M in **5.65a**). [b] Conversion and % **5.67a**, **5.68a**, **5.69a**, **5.70** and **5.71a** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [c] Full conversion [d] 32% conversion and a precipitate is formed during the reaction.

After optimization of the solvent, several additives were screened to either suppress the blank reaction, enhance the rate of the Cu-catalyzed reaction (again to overcome the blank reaction) and/or increase the selectivity towards the formation of S_N2' (**5.67a**) over the 1,4-addition (**5.69a**) product (Table 5.8). The addition of 0.1 equiv of the non-coordinating counterion BARF, used to favor formation of the Pd^{II} π-allyl intermediate in the Pd-catalyzed Tsuji-Trost allylation by separating the Cu-halide ion pair,[29] for the AAA gave mainly S_N2 product (**5.68a**, entry 2). This experiment, with BARF as additive, supports the mechanism involving a Cu^{III} σ-intermediate instead of a Cu^{III} π-intermediate proposed in paragraph 5.2 (Figure 5.3). Next, the use of several bromide containing Lewis acids as additive, ideally activating the bromide leaving group of **5.65a**, was tested. The use of these Lewis acids led to a decrease in formation of the S_N2' product (**5.67a**, entry 3 to 5). Furthermore, the use of several iodide sources as additive, presumably activating **5.65a** for AAA by in situ Br-I exchange, was tried. The use of the sparingly soluble NaI (entry 6) and LiI (entry 7) gave little γ-substitution; while the use of NBu_4I as additive gave no S_N2' product (**5.67a**) and mainly benzyl crotonate (**5.70**) was formed (entry 8). Finally, the use of the Lewis acidic AgCl (entry 9), again activating the bromide leaving group, led to a similar amount of S_N2' product **5.67a** compared to the reaction without this additive (entry 1).

Table 5.8. *Screening of additives for the Cu-TaniaPhos catalyzed AAA with EtMgBr.*[a,b]

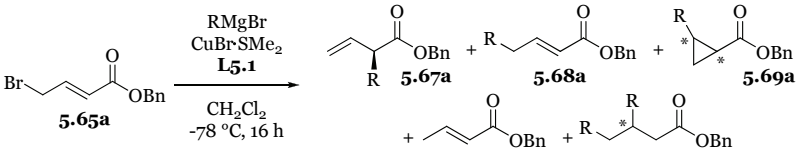


entry	additive	S_N2': **5.67a**[b]	S_N2: **5.68a**[b]	1,4-: **5.69a**[b]	**5.70**[b]
1	-	28%	27%	39%	<5%
2	BARF[d]	11%	42%	9%	18%
3	$ZnBr_2$	14%	34%	21%	9%
4	$MgBr_2$	12%	38%	15%	17%
5	LiBr	18%	40%	14%	15%
6	NaI	16%	37%	24%	10%
7	LiI	17%	22%	45%	9%
8	NBu_4I	-	-	18%	59%
9	AgCl	29%	41%	12%	18%

[a] Conditions: EtMgBr was added dropwise to a solution of **5.65a**, additive (0.5 equiv), EtMgBr (3.0 M in Et_2O, 1.2 equiv), ligand (5.5 mol%) and CuBr•SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **5.65a**). [b] In all cases the starting material was completely consumed. [c] Conversion and % **5.67a**, **5.68a**, **5.69a** and **5.70** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [d] 0.1 equiv of BARF was used.

Finally, for the AAA of substrate **5.65a** several Grignard reagents were screened (Table 5.9). The use of *i*BuMgBr for AAA of **5.65a** gave mainly S_N2 (**5.68a**) and 1,4-addition (**5.69a**) products (entry 2), while the use of hexylMgBr gave a mixture of products of which only benzyl crotonate (**5.70**) could be identified as main product (~50%). The use of PhMgBr led to low conversion in 16 h (entry 3). The main product using this particular Grignard reagent was the 1,4-addition product (**5.69a**). Finally, the use of the less reactive EtMgCl for AAA (entry 4) led to a better selectivity towards the S_N2'-product (**5.68a**) compared to the use of EtMgBr (entry 1). However, the preference for the formation of S_N2' (**5.68a**) over S_N2 (**5.69a**) product for EtMgCl is still insufficient for efficient AAA. Interestingly, for the AAA of **5.65a** with EtMgCl both the S_N2 (**5.69a**) and S_N2' (**5.68a**) product are formed via Cu-catalysis[xii] (see further paragraph 5.12).

Table 5.9. *Screening of Grignard reagents for Cu-TaniaPhos catalyzed AAA of* ***5.65a***.[a]



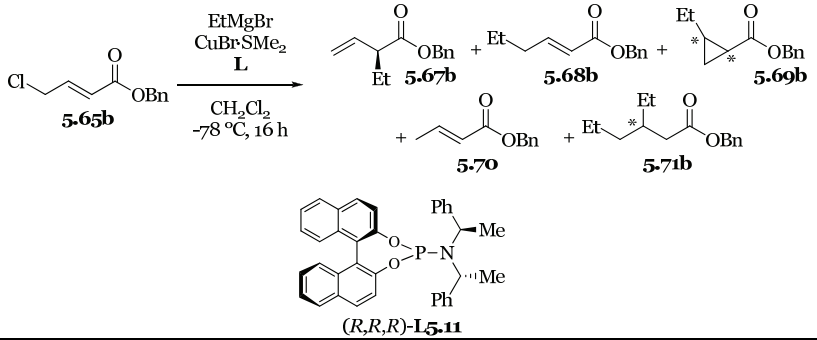
entry	RMgX	S_N2': **5.67a**[b]	S_N2: **5.68a**[b]	1,4-: **5.69a**[b]	**5.70**[b]	S_N2 and 1,4-: **5.71a**[b]
1	EtMgBr[c]	11%	40%	-	24%	26%
2	*i*BuMgBr[c]	7%	29%	27%	12%	-
3	PhMgBr[d]	-	2%	12%	-	-
4	EtMgCl[c]	34%	30%	7%	15%	8%

[a] Conditions: **5.65a** in solvent was added dropwise to a solution of EtMgBr (3.0 M in Et_2O, 1.2 equiv), ligand (5.25 mol%) and CuBr•SMe_2 (5 mol%) in solvent (0.2 M in **5.65a**). [b] Conversion and % **5.67a**, **5.68a**, **5.69a**, **5.70** and **5.71a** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [c] Full conversion. [d] In 40 h 30% conversion.

In addition to **5.65a**, other substrates were tested for AAA. First of all, substrate **5.65b**, incorporating a chloride leaving group, was subjected to AAA conditions. The use of a stoichiometric amount of ligand-free CuCN led to a mixture of products (Table 5.10, entry 1). Compared to the reaction of a stoichiometric amount of CuBr•SMe_2 with bromide substrate **5.65a**, for **5.65b** more S_N2' product (**5.67b**, 24% vs. 11% for **5.65a**) and no benzyl crotonate (**5.70**, 24% for **5.65a**) were obtained. Use of a catalytic amount of copper and either TaniaPhos (**L5.1**, entry 2) or JosiPhos (**L5.9**, entry 3) as ligand led to the 1,4-addition product **5.69b** as the main product in the AAA of **5.65b**. Using reversed JosiPhos (**L5.4**) the S_N2' product (**5.67b**) was obtained as main product in moderate ee (~50%, entry 4). Finally, the double addition product **5.71b** (subsequent S_N2 and 1,4-addition) was the main product using either diastereomer of a phosphoramidite ligand (**L5.3** and **L5.11**).

[xii] The blank reaction for EtMgCl with **5.65b**, performed as described in Table 5.5, gave full conversion and only 1,4-addition product (**5.69b**) in 16 h.

Table 5.10. Screening of several ligands for the AAA of **5.65b** with EtMgBr.[a,b]



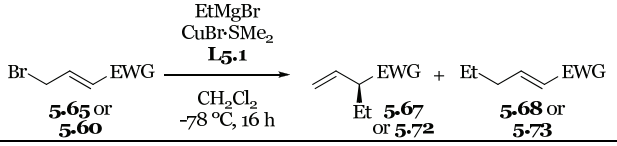
entry	ligand	S_N2': **5.67b**[c]	S_N2: **5.68b**[c]	1,4-: **5.69b**[c,d]	**5.70**[c]	S_N2 and 1,4-: **5.71b**[c]
1[e]	none[f]	24%	33%	-	-	42%
2	**L5.1**	7%	25%	58%	10%	-
3	**L5.9**	35%	1%	60%	-	4%
4	**L5.4**	76%[e,g]	-	5%	-	19%
5	**L5.4**[h]	55%	33%	2%	-	4%
6	**L5.3**	18%	-	-	21%	58%
7	**L5.11**	8%	-	-	16%	73%

[a] Conditions: EtMgBr (3.0 M in Et_2O, 1.2 equiv) was added dropwise to a solution of **5.65b**, ligand (5.25 mol%) and CuBr•SMe_2 (5 mol%) in solvent (0.2 M in **5.65b**). [b] In all cases the starting material was completely consumed. [c] % **5.67b**, **5.68b**, **5.69b**, **5.70** and **5.71b** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [d] A combination of cyclopropane **5.69b** and acyclic product (benzyl 4-chloro 3-methylpentanoate) was obtained. [e] Dropwise addition of substrate. [f] CuCN (1 equiv) was used and the reaction was performed at −40 °C. [g] The S_N2'-product was obtained in ~50% ee [h] 9.5 mol% of CuBr•SMe_2 and 10 mol% of ligand were used.

Furthermore, several substrates in which the acyl functionality was less electron withdrawing in order to reduce the amount of 1,4-addition product formed, were screened for the AAA using EtMgBr. Initially, the benzyl ester of **5.65a** was replaced by either an *i*Pr- or *t*Bu-ester (**5.65d** and **5.65h**). The use of these substrates in the AAA of EtMgBr gave a mixture of several volatile products. Furthermore, when the crude TBMDS ester **5.65i**[xiii] was subjected to typical AAA conditions, again a mixture of multiple products was obtained, concomitant in part with the cleavage of the oxygen-silicium bond. Further reduction of the strength of the electron withdrawing group, i.e. as an amide functionality (**5.65f** and **5.65g**), gave the S_N2 product (**5.69f**, **5.69g**) as main product (Tabel 5.11, next page, entry 1 and 2). Then finally, the use of bromocrotonic acid **5.60** as substrate for AAA, deprotonated with EtMgBr, gave more promising results (entry 3). However, further optimization (deprotonation with either CaH_2, KO*t*Bu, *n*BuLi or NaH) did not lead to improved selectivity towards γ-substitution.

[xiii] See paragraph 5.5.

Table 5.11. *Use of several substrates in AAA using EtMgBr.*[a]

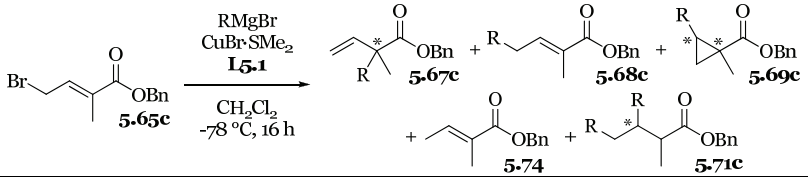


entry	substrate	EWG	conversion[c]	S_N2'[b]	S_N2[b]
1	**5.65f**	CONHBn	26%	**5.67f**: 7%	**5.68f**: 14%
2	**5.65g**	COpiperidine	full	**5.67g**: 22%	**5.68g**: 41%
3	**5.60**	COOH[c]	full	**5.72**: 57%	**5.73**: 43%

[a] Conditions: EtMgBr (3.0 M in Et_2O, 1.2 equiv) was added dropwise to a solution of substrate, ligand (5.25 mol%) and CuBr•SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in substrate). [b] Conversion and % **5.67**, **5.68**, **5.72** and **5.73** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [c] 2.5 equiv of EtMgBr was used.

α-Substituted 4-halocrotonates have been successfully alkylated by Hoveyda and co-workers using Zn-reagents.[23b] To test whether these substrates are also suitable candidates for the Cu-catalyzed AAA with Grignard reagents, **5.65c** was subjected to AAA with either MeMgBr and EtMgBr (Table 5.12). The use of MeMgBr gave mainly S_N2 product (**5.68c**), 1,4-addition product (**5.69c**), benzyl 2-methylcrotonate (**5.74**) and some other products with higher molecular mass (entry 1). Finally, the main product for the AAA with EtMgBr was the S_N2 product **5.68k** (entry 2).

Table 5.12. *Attempted AAA of 2-methyl 4-bromocrotonate (**5.65c**) using Grignard reagents.*[a,b]



entry	RMgBr	product	S_N2': **5.67c**[c]	S_N2: **5.68c**[c]	1,4-: **5.69c**[c]	**5.74**[c]	S_N2 and 1,4-: **5.71c**[c]
1	Me[d]	c	2%[e]	13%	15%	12%	-
2	Et	k	12%[f]	46%	5%	17%	2%

[a] Conditions: RMgBr (3.0 M in Et_2O, 1.2 equiv) was added dropwise to a solution of **5.65c**, ligand (5.25 mol%) and CuBr•SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **5.65c**). [b] In all cases the starting material was completely consumed. [c] % **5.67c**, **5.68c**, **5.69c**, **5.74** and **5.71c** are determined by GC-MS and correlate approximately with the ratio observed by ^{1}H-NMR. [d] Full conversion in 40 h. [e] 30% products with higher molecular mass than the drawn products are obtained. [f] 9% of product of subsequent reduction and 1,4-addition was obtained.

5.8 Formation of benzyl crotonate

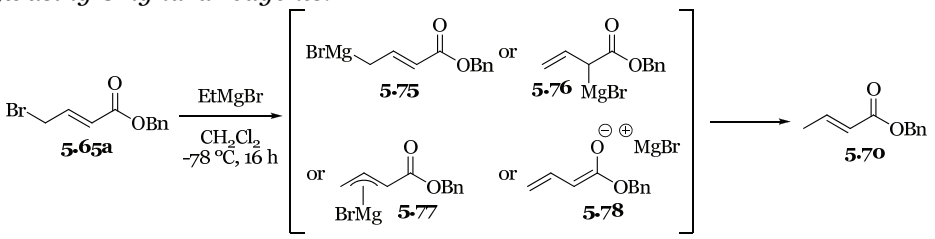
One of the side-products of the reaction of EtMgBr with benzyl 4-bromocrotonate (**5.65a**) is benzyl crotonate (**5.70**). Especially when the substrate was added slowly to a solution of EtMgBr and catalyst (in 0.5 h using a syringe pump), benzyl crotonate was formed in substantial amounts (see also Table 5.6, entry 2, 3, 5, 7 and 8). Preliminary results show that at higher temperature, for slow addition of the substrate to an excess of Grignard reagent, more of the benzyl crotonate is formed.

A likely explanation for the formation of **5.70** is a Mg-Br exchange, forming the functionalized Grignard reagent **5.75**, which is protonated during work-up (Scheme 5.15). The Grignard reagent can also be depicted in three tautomeric structures, either, as secondary Grignard reagent (**5.76**), as η³ allylic Grignard reagent (**5.77**) or as dienolate (**5.78**). The exact nature of this reagent needs further study.

Although the pathway for the formation of benzyl crotonate[xiv] needs more study, the formation of traces of hexylbromide[xv] in the reaction of an excess of hexylMgBr with substrate **5.65a** supports the Mg-Br exchange mechanism (Scheme 5.16a, next page). Furthermore, the proposed pathway is supported by the formation of D-incorporated benzyl crotonate (1D-**5.70**, relative abundance D_1-benzyl crotonate 100%; all-H benzyl crotonate ~10%) when the reaction of *i*PrMgCl•LiCl with benzyl crotonate is quenched by MeOD (Scheme 5.16b, next page).[xvi]

The reactivity of the formed functionalized Grignard reagent (or dienolate) is rather low. In an attempt to trap the formed reagent with benzaldehyde, the product **5.79** was not found (Scheme 5.16c, next page). Further experiments are needed to determine the possible synthetic use of this functionalized Grignard reagent (or dienolate).

Scheme 5.15. *Tentative pathway for the formation of benzyl crotonate **5.70** from **5.65a** using Grignard reagents.*

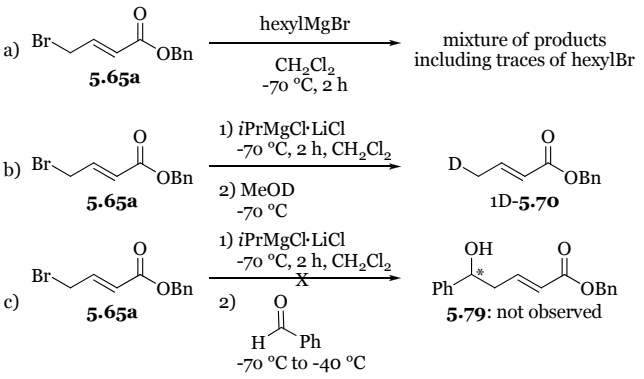


[xiv] An alternative mechanism via β-hydride transfer seems less likely in view of the formation of hexylbromide (vide infra), but cannot be excluded. For an example of β-hydride transfer with Grignard reagents see: M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998-9999.

[xv] The Grignard reagent does not contain hexylbromide as shown by quenching of hexylMgBr with MeOH in CH_2Cl_2 at -70 °C.

[xvi] Quenching by MeOD of a mixture of ethyl crotonate and iPrMgCl•LiCl, as control experiment, gave the following masses by GC-MS for "unreacted" ethyl crotonate 114 (relative abundance: 100%, $C_6H_{10}O_2$), 115 (~30%), 116 (~70%), 117 (~10%). This result is unexpected and needs further investigation.

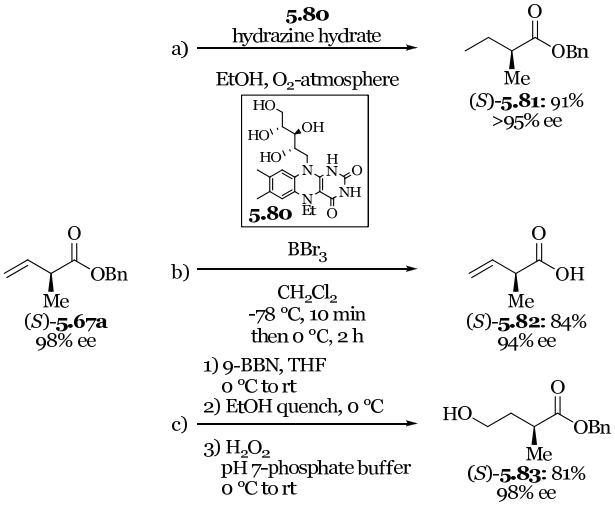
Scheme 5.16. *Formation of benzyl crotonate from* ***5.65a*** *using Grignard reagents via a Mg-Br exchange.*



5.9 Synthesis of chiral multifunctional building blocks with a single stereogenic center

Elaboration of the products to multifunctional building blocks proved challenging due to the ready isomerization of the β,γ-unsaturated ester to the conjugated α,β-unsaturated ester. However, we were able to obtain several chiral building blocks derived from (*S*)-**5.67a** in high ee and yield (Scheme 5.17, 5.18, 5.19, 5.22, 5.23 and 5.24 and Table 5.17).

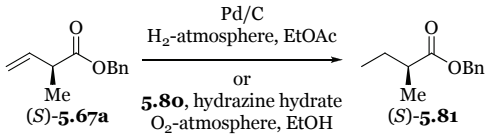
Scheme 5.17. *Synthesis of multifunctional building blocks incorporating a single stereogenic center starting from olefin* ***5.67a****.*



Conditions: a) **5.67a**, **5.80** (20 mol%), hydrazine hydrate (10 equiv), EtOH (0.11 M in **5.67a**), O_2-atmosphere, rt, 2 h. b) **5.67a**, BBr_3 (1.5 equiv), CH_2Cl_2 (0.22 M in **5.67a**), −78 °C, 10 min, 0 °C, 2 h. c) 1) **5.67**, 9-BBN (0.5 M solution in THF, 2.5 equiv), THF (total 0.29 M in **5.67a**), 0 °C to rt, 1.5 h; 2) EtOH (3.5 equiv), 0 °C; 3) H_2O_2 (~4.7 equiv), phosphate buffer pH 7.0 (total THF and H_2O 0.13M in **5.67a**), 0 °C to rt, 1 h.

First of all, we focused on orthogonally reducing either the olefin or liberating the carboxylic acid (Scheme 5.17a and b). The reduced protected chiral α-Me substituted esters like (*S*)-**5.81** are highly warranted building blocks and have been used previously for the synthesis of a pheromone of the male mouse, *Mus musculus*,[30] and the synthesis of several fragrances.[31] We were able to reduce the olefin in high yield retaining the stereochemical integrity of the α-Me center, without deprotection of the ester (Scheme 5.17a).[32,33] In initial attempts employing hydrogenation catalyzed by Pd on carbon we observed substantial isomerization (Table 5.13, entry 1). Reducing the amount of Pd on carbon and degassing of the solvent (EtOAc) still gave substantial isomerization and low conversion (entry 2). Using our recently developed method for olefin reduction by diimide, generated *in situ* from hydrazine and a cheap vitamin B_2 derivative **5.80**,[34] we obtained full conversion with only traces of isomerization (entry 3). However, using 20 equiv of hydrazine the formation of benzylalcohol was observed, indicating hydrazide formation. To prevent the reaction of hydrazine with the ester moiety, the amount of this reagent used in the reaction was decreased (entry 4). The use of 7.5 equiv of hydrazine did not give full conversion, even when more catalyst was used (entry 5). To improve the conversion several addition modes were investigated. Although the slow addition of hydrazine to the reaction mixture gave low conversion (entry 6), a slow addition protocol of both 10 equiv of hydrazine and 20 mol% of catalyst to the substrate gave full conversion (entry 7). The results described in the last two entries of Table 5.13 lead to the conclusion that the catalyst **5.80** degrades under the reaction conditions.

Table 5.13. *Reduction of the β,γ-unsaturated olefin of* ***5.67a***.[a]



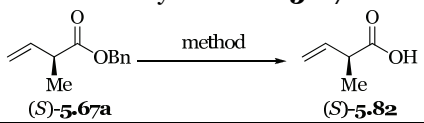
entry	reduction method	hydrazine	time	reduction[b]	isomerization[b]
1	Pd/C (0.25%)	-	1 h	full	24%
2	Pd/C (0.1%)[c]	-	1 h	40%	9%
3	**5.80** (5%)	20 equiv	4 h	full[d]	<5%
4	**5.80** (5%)	7.5 equiv	4 h	~90%	<5%
5	**5.80** (20%)	7.5 equiv	2 h	81%	3%
6	**5.80** (20%)	7.5 equiv	2 h	48%	5%
7	**5.80** (20%)	10 equiv[ed]	2 h	full	<5%

[a] Conditions: **5.67a**, Pd/C (5 wt%), EtOAc (0.2 M in **5.67a**), H_2 atmosphere, rt or **5.67a** (1 equiv), **5.80**, hydrazine hydrate, EtOH (0.11 M in **5.67a**), O_2-atmosphere, rt. [b] % reduction and isomerization were determined by GC-MS and correlate with the ratio observed by ^{1}H-NMR. [c] Degassed EtOAc was used. [d] BnOH (10 mol%) observed. [e] Slow addition of **5.80** and hydrazine hydrate.

Vice versa, deprotection of the carboxylic acid leaving the olefin intact, proceeded in good yield with only marginal loss of enantiopurity (Scheme 5.17b).[35] Initial attempts to deprotect (*S*)-**5.67a** using base (Table 5.14, next page, entries 1, 2 and 3) gave low conversion. Using Li^+ as counterion, a higher conversion was obtained with extensive amounts of isomerization (entry 4). The use of H_2O_2 to prepare in-situ the more nucleophilic hydroperoxide anion, gave lower conversion

and a higher degree of isomerization (entries 5 and 6). Acidic saponification either gave low conversion (entry 7) or extensive amounts of isomerization (entries 8 and 9). A low conversion was also obtained in the combined use of a catalytic amount of NaCN, used to prepare an activated intermediate acyl cyanide, and aq base (entry 10). Lewis acidic mediated deprotection using $AlCl_3$ gave extensive isomerization, with low conversion (entry 11). Lewis acidic mediated deprotection employing BBr_3 at low temperature (−78 °C, entry 12) or using BBr_3•SMe_2 (entry 13) or BCl_3 (entry 14) at higher temperature (−78 to 0 °C) gave a clean reaction, with extensive amount of isomerization. Finally, the use of BBr_3 at higher temperatures (−78 to 0 °C) still gave a clean reaction with only trace amounts of the isomerized product (entry 15).[xvii] Previously, the racemic building block **5.82** has been used for the synthesis of racemic multistriatin.[36]

Table 5.14. Deprotection of the carboxylic acid of **5.67a**.[a]



(*S*)-**5.67a** (*S*)-**5.82**

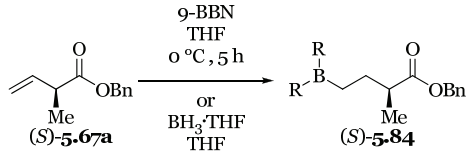
entry	method	conversion[b]	isomerization[b]
1	$NaHCO_3$	<5%	-
2	Na_2CO_3	<5%	-
3	KOH	<5%	-
4	LiOH	>95%	53%
5	LiOH, H_2O_2	57%	89%
6	LiOH, LiCl, H_2O_2	78%	81%
7	HCl	<5%	-
8	acidic alumina, MW	>95%	81%
9	TFA	35%	30%
10	NaCN, $NaHCO_3$	<5%	-
11	$AlCl_3$, anisole	13%	~50%
12	BBr_3	>95%	25%
13	BBr_3•SMe_2	>95%	>95%
14	BCl_3	>95%	25%
15	BBr_3	>95%	<5%

[a] Conditions: **5.67a**, $NaHCO_3$ (4 equiv), H_2O (0.1 M in **5.67a**), rt, 64 h or **5.67a**, Na_2CO_3 (saturated aq solution 10 mL/mmol **5.67a**), rt, 64 h or **5.67a**, KOH (1 equiv), H_2O (0.1 M in **5.67a**), rt, 16 h or **5.67a**, LiOH (3 equiv), H_2O/THF (4/1, 0.1 M in **5.67a**), rt, 16 h or **5.67a**, LiOH (3 equiv), H_2O_2 (6 equiv), H_2O/THF (4/1, 0.1 M in **5.67a**), rt, 16 h or **5.67a**, LiOH (3 equiv), LiCl (3 equiv), H_2O_2 (6 equiv), H_2O/THF (4/1, 0.1 M in **5.67a**), rt, 6 h or **5.67a**, HCl (40 equiv), H_2O (0.1 M in **5.67a**), rt, 16 h or **5.67a**, acidic Al_2O_3 (10 g/mmol **5.67a**), microwave, 130 °C, 7 min or **5.67a**, TFA (7 equiv), H_2O (0.1 M in **5.67a**), rt, 64 h or **5.67a**, NaCN (15 mol%), $NaHCO_3$ (5 equiv), H_2O (0.1 M in **5.67a**), rt, 16 h or **5.67a**, $AlCl_3$ (2 equiv), anisole (4 equiv), CH_2Cl_2 (0.22 M in **5.67a**), rt, 24 h or **5.67a**, BBr_3 (1.1 equiv), CH_2Cl_2 (0.22 M in **5.67a**), −78 °C, 1 h, then rt, 1 h or **5.67a**, BBr_3•SMe_2 (1.5 equiv), CH_2Cl_2 (0.22 M in **5.67a**), −78 °C, 10 min, 0 °C, 2 h or **5.67a**, BCl_3 (1.5 equiv), CH_2Cl_2 (0.22 M in **5.67a**), −78 °C, 10 min, 0 °C, 2 h or **5.67a**, BBr_3 (1.5 equiv), CH_2Cl_2 (0.22 M in **5.67a**), −78 °C, 10 min, 0 °C, 2 h. [b] % conversion and isomerization were determined by ^{1}H-NMR.

[xvii] With respect to the higher *ee* measured for the iodolactonization products (*vide infra*) there might be a small impurity under the minor peak on the chiral GC and the ee might be higher.

Another warranted building block could be obtained *via* a hydroboration-oxidation sequence leading to the terminal alcohol (*S*)-**5.83**.[37] This compound has been used previously for the synthesis of sea food odours[37a] and the synthesis of four stereoisomers of the phytophthora α1 mating hormone.[37d] Using an excess of 9-BBN, followed by subsequent oxidation at pH 7 with strict control of the reaction time, (*S*)-**5.83** was obtained in good yield (Scheme 5.17c). Presumably the first equivalent of 9-BBN coordinates to the ester as witnessed from the low conversion with 1.2 and 1.5 equivalent of this reagent (Table 5.15, entry 1, 2). Furthermore, extended reaction times or a basic reaction medium in the oxidation step causes lactonization.[xviii] Using the BH_3•THF complex for hydroboration, instead of 9-BBN, again the first equiv of BH_3•THF coordinates to the ester (entry 4, 5) and only with 1.5 equiv full conversion of **5.67a** to the borane[xix] is observed (entry 6). However, the hydroboration-oxidation sequence using BH_3•THF gave only lactonized product.

Table 5.15. *Optimization of stoichiometry for the hydroboration of* ***5.67a***.[a]



entry	reagent	equiv B-reagent	conversion
1	9-BBN	1.2	traces[b]
2	9-BBN	1.5	3%[b]
3	9-BBN	2.0	>95%[b]
4	BH_3•THF	0.5	<5%[c]
5	BH_3•THF	1.0	21%[c]
6	BH_3•THF	1.5	>95%[c]

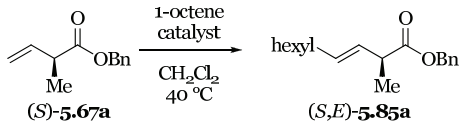
[a] Conditions: **5.67a**, 9-BBN (0.5 M solution in THF), THF (total 0.29 M in **5.67a**) or **5.67a**, BH_3•THF (1 M solution in THF), THF (total 0.33 M in **5.67a**). [b] % conversion from (*S*)-**5.67a** to (*S*)-**5.84** was determined by GC-MS. [c] % conversion from (*S*)-**5.67a** to (*S*)-**5.81** was determined by GC-MS.

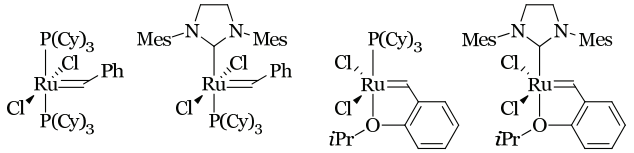
Cross metathesis (CM) starting from building block **5.67a** has been used previously to prepare (*R*)-elenic acid[23a] by Hoveyda and co-workers. This particular CM with a challenging 2,2-disubstituted terminal olefin yielded the intended product in low conversion[23a] We envisioned that CM could modularly produce a variety of α-Me esters.[38] Initial attempts using CM-catalysts gave either extensive isomerization (Table 5.16, next page, entries 1, 2 and 4) or low conversion (entry 3). However, employing 2,6-dichlorobenzoquinone as additive,[39] presumably preventing the formation of RuH,[39a] the *E*-CM products were obtained in good conversion and only traces of isomerization product were observed (entry 5).

Using these optimized conditions, a variety of olefins could be coupled to **5.67a** (Table 5.17, next page, entry 1, 3 and 4). Coupling, however, of an olefin bearing an unprotected hydroxyl group gave extensive isomerization (entry 2).

[xviii] Storage of **5.83** for extended time at −20 °C (checked after 7 d) also gives lactonization.
[xix] The reduced product **5.81** is found by GC-MS.

Table 5.16. *Ligand and additive screening for the cross metathesis of* ***5.67a***.[a]

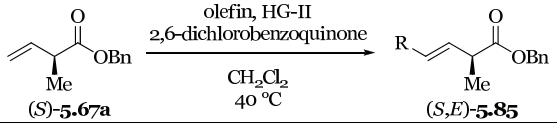




entry	catalyst	additive	conversion[b]	isomerization[b]
1	Grubbs I	-	62%	86%
2	Grubbs II	-	92%	27%
3	Hoveyda-Grubbs I	-	68%	3%
4	Hoveyda-Grubbs II	-	full	76%
5	Hoveyda-Grubbs II	Cl_2BQ	full	<5%

[a] Conditions: **5.67a**, 1-octene (2 equiv), catalyst (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH_2Cl_2 (0.25 M in **5.67a**), 40 °C, 16 h. [b] % conversion and isomerization were determined by GC-MS and correlate with the ratio observed by ^{1}H-NMR.

Table 5.17. *Cross metathesis of* ***5.67a*** *with a variety of olefins.*[a]

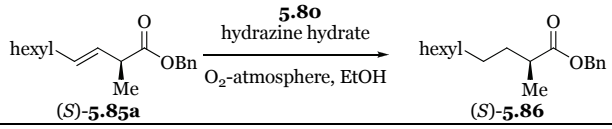


entry	olefin	product	time	yield	isomerization[b]
1		**5.85a**	8 h	84%	<5%
2[c]	HO	**5.85b**	16 h	nd (91%)[d]	91%
3	TBDPSO	**5.85c**	8 h	66%	<5%
4	Br Br	**5.85d**	16 h	73%[e]	<5%

[a] Conditions: **5.67a**, olefin (2 equiv), HG-II (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH_2Cl_2 (0.25 M in **5.67a**), 40 °C, 16 h. [b] % isomerization is determined by ^{1}H-NMR. [c] 10 mol% HG-II and 20 mol% 2,6-dichlorobenzoquinone were used. [d] % conversion, determined by GC-MS. [e] Product was obtained in 96% ee.

A substrate class closely related to the cross metathesis products is the α-Me substituted saturated esters.[40] These building blocks have been previously used for the synthesis of an alarm pheromone of *Atta texana*,[41] a high-potency sweetener NC-00637,[40a] and candidates for a tuberculosis vaccine.[42] We envisioned that these building blocks could be modularly constructed by a CM-olefin reduction sequence from **5.67a**. However, the reduction of the internal olefin is more challenging than that of the terminal olefin (vide supra). Using 50 mol% of catalyst **5.81** and 15 equiv of hydrazine gave 65% conversion (Table 5.18, entry 1). Further increase of the amount of hydrazine (entry 2) and catalyst (entry 3) with increased addition time of both catalyst and reagent led to a higher conversion. Finally, with 1 equiv of **5.81** and 40 equiv of hydrazine almost full conversion was obtained (entry 4). With these optimized conditions[34] for the non-transition metal mediated reaction we were able to obtain (*S*)-**5.86** in 89% conversion and 75% yield (Scheme 5.18) illustrating the possibility of assembling the highly warranted α-Me substituted esters using AAA.

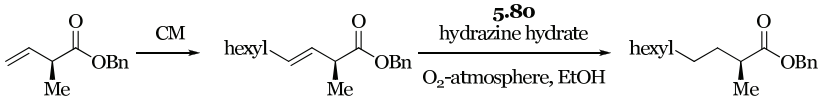
Table 5.18. *Reduction of internal β,γ-unsaturated olefin of* ***5.85a****.*[a]



entry	**5.81**	hydrazine	addition time	reduction[b]	isomerization[b]
1	0.5 equiv	15 equiv	2 h	65%	<5%
2	0.5 equiv	30 equiv	2.5 h	76%	<5%
3	1.0 equiv	40 equiv	5 h	81%	<5%
4	1.0 equiv	54 equiv	5 h	89%	<5%

[a] Conditions: **5.85a**, **5.80** (1 equiv), hydrazine hydrate, EtOH (0.11 M in **5.85a**), rt, O_2-atmosphere, slow addition under vigorous stirring, additional 1 h vigorous stirring.

Scheme 5.18. *Synthesis of α-Me substituted esters.*



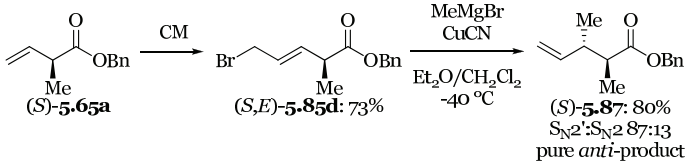
Conditions: see Table 5.18 for CM. **5.85a**, 9 (1 equiv), hydrazine hydrate (50 equiv), EtOH (0.11 M in **5.85a**), rt, O_2-atmosphere, 5 h addition under vigorous stirring, additional 1 h vigorous stirring.

5.10 Synthesis of chiral multifunctional building blocks with multiple stereogenic centers

After completing the synthesis of a number of building blocks with a single stereogenic center, we turned our attention to preparation of building blocks with multiple stereogenic centers. To obtain *anti*-vicinal dimethyl motifs, the CM product (*S*,*E*)-**5.85d** was converted to (*S*)-**5.87** in good yield and reasonable regioselectivity (Scheme 5.19).[43]

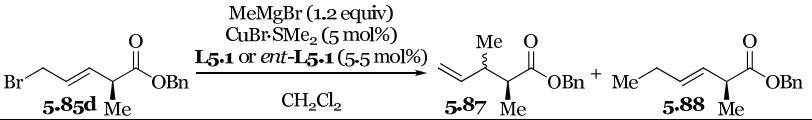
To obtain the *syn*-vicinal dimethyl motif the AAA of **5.85d** using catalytic amounts of Cu-TaniaPhos as chiral catalyst was studied (Table 5.19, next page). First, the reaction with the (*R*,*R*)-TaniaPhos ligand (**L5.1**), leading to *anti*-vicinal dimethyl product **5.87**, was explored. Using normal AAA-conditions the reaction was remarkably slow and gave moderate γ-selectivity (entry 1). Performing the reaction at −80 °C gave selectively the S_N2' product with traces of unreacted starting material (entry 2). However, the use of (*S*,*S*)-TaniaPhos (*ent*-**L5.1**), presumably leading to the product with a *syn*-vicinal dimethyl motif, gave predominantly the S_N2 product (entry 3). To prepare *syn*-vicinal dimethyl motifs the method of choice is subsequent AAA with MeMgBr, cross metathesis of ethyl thioacrylate and ACA of MeMgBr.[5d]

Scheme 5.19. *Synthesis of an anti-vicinal dimethyl motif.*[a]



[a] Conditions: See Table 5.17 for CM. **5.85d**, MeMgBr (2 equiv), CuCN (2 equiv), Et_2O/CH_2Cl_2 (2:3, 0.1 M in **5.85d**), −40 °C, 16 h.

Table 5.19. *Synthesis of vicinal dimethyl motifs by asymmetric catalysis.*[a]



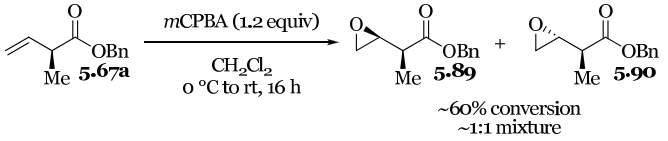
entry	L	temperature	reaction time	conversion	*anti*/*syn*-**5.87**[b]	S_N2':S_N2[c]
1	**L5.1**	-78 °C	3 days	full	*anti*	81:19
2	**L5.1**[d]	-80 °C	3 days	97 %	*anti*	97:3
3	*ent*-**L5.1**	-80 °C	40 h	full	*syn*	22:78

[a] Conditions: **5.85d** in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O, 1.2 equiv), **L5.1** (5.5 mol%) and CuBr•SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **5.85d**). [b] Exclusively *anti*- or *syn*-product was obtained. [c] Determined by NMR spectroscopy. [d] (*R*,*R*)-**L5.1** (11 mol%) and CuBr•SMe_2 (10 mol%) were used.

A very interesting motif in the context of natural product synthesis is the propionate unit. An initial attempt to selectively obtain the *anti*-propionate motif using epoxidation, by chiral induction of the substrate, gave an approximately 1:1 mixture of *syn*- and *anti*-product (Scheme 5.20).

To obtain selectively either the *syn*- or *anti*-propionate motif asymmetric catalytic *cis*-dihydroxylation was explored. Using typical Sharpless asymmetric dihydroxylation conditions, several ligands were screened for the preparation of this structural entity (Table 5.20).[44] Using methylsulfonamide[45] to speed up the dihydroxylation of **5.67a**, ligand **L5.13** proved superior for the preparation of the *anti* β-hydroxy γ-butyrolactone (entry 2) and **L5.14** gave the best results for the *syn* β-hydroxy γ-butyrolactone (entry 3).[xx] In all cases the lactonized products were obtained as a single diastereomer in reasonable yields and high ee (Scheme 5.21). The propionate building blocks have been used previously for the syntheses of (−)-α-multistriatin[43b] and apoptolidinone.[46]

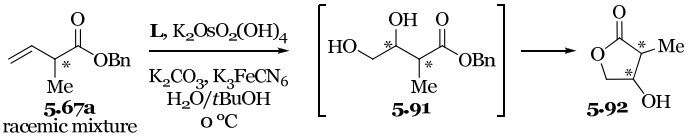
Scheme 5.20. *Epoxidation of* ***5.67a****.*[a]

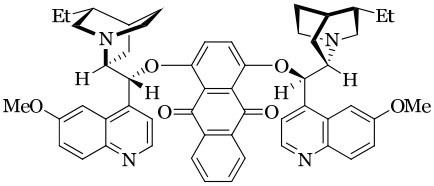


[a] Conditions: **5.67a**, *m*CPBA (1.2 equiv), CH_2Cl_2 (0.1 M in **5.67a**), 0 °C to rt, 16 h.

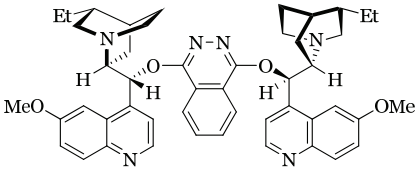
[xx] The observed enantioselectivities in this reaction are representative for terminal olefins.

Table 5.20. *Screening of ligands for the asymmetric dihydroxylation of a racemic mixture of* ***5.67a***.[a]

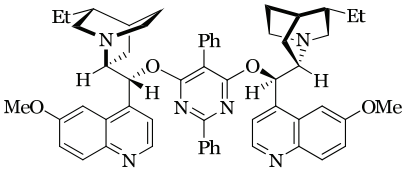




L5.12: $(DHQ)_2AQN$



L5.13: $(DHQ)_2Phal$

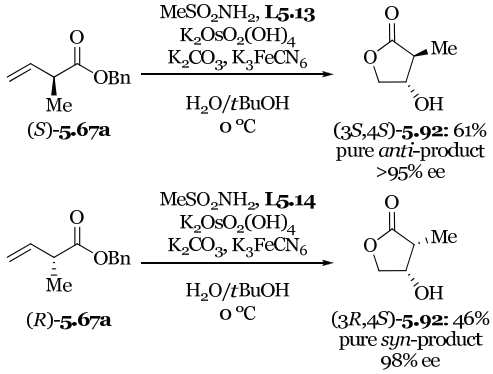


L5.14: $(DHQ)_2Pyr$

entry	ligand	*ee anti*[b]	*ee syn*[b]
1	**L5.12**	60%	60%
2	**L5.13**[c]	85%	64%
3	**L5.14**[c]	70%	70%

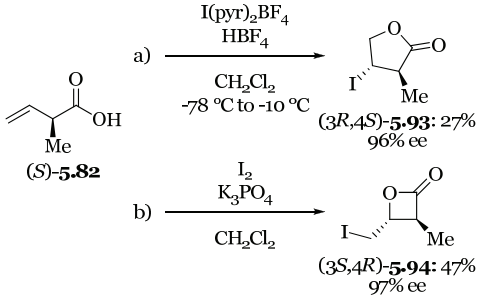
[a] Conditions: **5.67a**, **L** (2.5 mol%), $K_2OsO_2(OH)_4$ (1 mol%), K_2CO_3 (3 equiv), K_3FeCN_6 (3 equiv), H_2O/*t*-BuOH (1:1, 0.1 M in **5.67a**), 0 °C, 16 h. [b] Determined by chiral GC. *ee anti*: 100x({(3*S*,3*R*)-**5.92** – (3*S*,3*R*)-**5.92**} / [(3*S*,4*S*)-**5.92** + (3*S*,3*R*)-**5.92**]). *ee syn*: 100x({(3*R*,3*R*)-**5.92** – (3*R*,4*S*)-**5.92**} / [(3*R*,3*R*)-**5.92**) + (3*R*,4*S*)-**5.92**]). [c] $MeSO_2NH_2$ (1 equiv) was used.

Scheme 5.21. *Synthesis of lactonized propionate motifs.*[a]



[a] For conditions see Table 5.20.

Scheme 5.22. *Iodolactonization of* ***5.82*** *leading to 5- and 4-membered lactones.*[a]



[a] Conditions: a) **5.82**, $I(pyr)_2BF_4$ (1.1 equiv), HBF4 (1.5 equiv), CH_2Cl_2 (0.03 M in **5.82**), −78 °C to -10 °C, 1.5 h. b) **5.82**, I_2 (5 equiv), K_3PO_4 (5 equiv), CH_2Cl_2 (9.5 mM in **5.82**), rt, 40 h.

Finally, when the deprotected β,γ-unsaturated carboxylic acid (*S*)-**5.82** was subjected to iodolactonization using Barluenga's reagent[47,xxi] the 5-membered lactone (**5.93**, Scheme 5.22a) was obtained albeit in a low yield.[48] Performing the iodolactonization employing I_2 and K_3PO_4 in CH_2Cl_2 the 4-membered lactone (**5.94**, Scheme 5.22b) was obtained.[49,xxii]

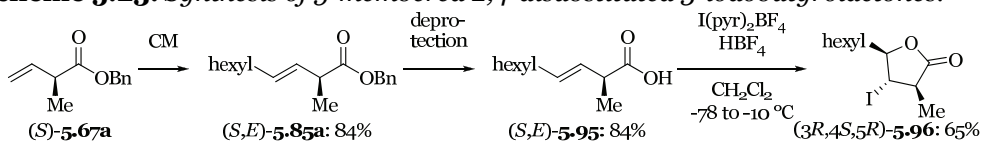
2,4-Disubstituted 3-butyrolactones[50] (**5.96**) are interesting building blocks for natural product synthesis and have been used for example in the synthesis of jasplakinolide.[51] We envisioned constructing these highly versatile structures with three contiguous stereogenic centers by an AAA-CM-carboxylic acid deprotection-iodolactonization sequence. We managed to obtain **5.96** in good yield as the single 3,4-*trans*-4,5-*trans* diastereomer[xxi,xxiii] (Scheme 5.22) illustrating the potential of these transformations to modularly construct 5-membered 2,4-disubstituted 3-iodobutyrolactones.

[xxi] According to literature, the 5-membered lactone products possess the all-*trans* configuration: J.-M. Garnier, S. Robin, R. Guillot, G. Rousseau, *Tetrahedron: Asymmetry* **2007**, *18*, 1434-1442. In NOESY-NMR experiments for **5.93** {(3*R*,4*S*)-4-iodo-3-methyldihydrofuran-2(3H)-one} we found a stronger interaction between one of the C5 protons and the C4 proton and a weaker interaction with the other C5 proton and the C4 proton. The weaker interaction is as strong as the interaction of the protons of C4 and C3. For **5.96** {(3*R*,4*S*,5*R*)-5-hexyl-4-iodo-3-methyldihydrofuran-2(3*H*)-one} we found a weak interaction between the protons of C5 and C4 and an interaction similar in strength for the C4 and C3 protons. In combination with the expected *trans*-configuration for the protons of C4 and C5 arising from *anti*-addition of the carboxylate on the iodonium intermediate this most likely indicates an all-*trans* configuration of both **5.93** and **5.96**.

[xxii] At higher concentration using the same reagents, the 5-membered lactone was obtained in low yield. This product is presumably formed by iodination of the olefin followed by S_N2 attack of the carboxylate on the terminal iodoalkane.

[xxiii] Using **5.95**, I_2 (5 equiv), K_3PO_4 (5 equiv), CH_2Cl_2 (9.5 mM in **5.95**), rt, 16 h the 5-membered product **5.96** was obtained in 77% yield. However, this yield was calculated from an impure spectrum containing an inseparable C_{11}-phthalate from the CH_2Cl_2 used for the work-up of this reaction.

Scheme 5.23. *Synthesis of 5-membered 2,4-disubstituted 3-iodobutyrolactones.*[a]



(*S*)-**5.67a** (*S*,*E*)-**5.85a**: 84% (*S*,*E*)-**5.95**: 84% (3*R*,4*S*,5*R*)-**5.96**: 65%

[a] Conditions: See Table 5.18 for CM. See Scheme 5.17b for deprotection. **5.95**, $I(pyr)_2BF_4$ (1.1 equiv), HBF_4 (1.5 equiv), CH_2Cl_2 (0.03 M in **5.95**), −78 °C to −10 °C, 1.5 h.

5.11 Conclusion

In summary, we have developed a highly enantioselective allylic alkylation of benzyl 4-bromocrotonates leading to chiral α-Me substituted esters. These products have been successfully elaborated to a variety of chiral multifunctional building blocks without significant loss of stereochemical integrity at the stereogenic center. In this way, highly enantioenriched branched esters and acids, as well as *anti*-vicinal dimethyl units and hydroxyl- or iodosubstituted lactones were prepared. Allylic alkylation of 4-halocrotonates with several, more reactive, alkyl Grignard reagents led to mixture of S_N2, S_N2', 1,4-addition and dehalogenated products.

5.12 Perspective and outlook

Although the synthesis of α-Me esters via Cu-catalysis with organometallic reagents was already known,[23] the methodology described in this chapter is a significant improvement. Especially, the use of nearly stoichiometric amounts of MeMgBr, instead of the use of 6 equiv of Me_2Zn, with the transfer of all alkyl groups of the organometallic reagent is an important advancement. Furthermore, the use of only 1 mol% of a Cu-catalyst with a commercially available ligand will allow for ready use of the described method in academia. The potential use of the AAA of 4-halocrotonates in industry will be hampered by the low temperature employed. However, possibly the described transformation might be performed at higher temperatures without major loss of selectivity.[5c]

The explored synthetic transformations on the AAA-product **5.67a** show great potential for the elaboration of related AAA products. The iodolactonization might be performed on related AAA products with either a hydroxy, a carboxylic acid, an amine or an amide functionality and an internal or terminal olefin to yield a variety of enantioenriched lactones, lactams and related heterocycles. Furthermore, the consecutive AAA-Sharpless *cis* dihydroxylation sequence will allow straight-forward, non aldol-based,[52] synthetic routes for the construction of bifunctional *syn*- or *anti*-propionate units from a variety of AAA products. To further optimize the synthesis of these highly warranted motifs, one could use internal olefins (the products from an AAA and consecutive CM), which are known to give higher enantioselectivity for *cis* dihydroxylation. Presumably, a subsequent AAA combined with a CM of a vinyl silane[53] and finally a tandem

cis dihydroxylation-Peterson olefination[54,xxiv] will give ready access to functionalized propionate motifs.

Finally, the irreproducibility of the reaction of reactive alkyl Grignard reagents with 4-halocrotonates hampers optimization of the (Cu-catalyzed) AAA of 4-halocrotonates with those Grignard reagents. Despite the variety of employed conditions reported in this chapter, further research might give access to α-alkyl esters via AAA. To this extent, either phosphoramidite ligands might be screened for the AAA of benzyl 4-chlorocrotonate and/or several conditions might be screened for the AAA of benzyl 4-chlorocrotonate with EtMgCl.

Two interesting serendipitous findings in the progress of the research described in this chapter are the formation of benzyl crotonate from benzyl 4-bromocrotonate (paragraph 5.8) and the slow, highly selective, AAA of sterically hindered δ-Me substituted AA substrates (Table 5.19, paragraph 5.10). The formation of benzyl crotonate might proceed via a rare[xxv] highly functionalized Grignard reagent, which might be not only highly versatile in synthesis, but might also give further insight in Br-Mg exchange reactions. Finally, the slow but highly selective conversion of δ-Me substituted AA substrates might allow for the characterization of intermediates by low temperature NMR.

5.13 Acknowledgement

Dr. T. Jerphagnon is acknowledged for fruitful discussions concerning the mechanism described in paragraph 5.2. Dr. B. Maciá is acknowledged for part of the screening results described in paragraph 5.7.

[xxiv] Alternatively CM of a vinylphosphate reagent/tandem cisdihydroxylation-Horner-Wadsworth-Emmons reaction will give access to the same building blocks.

[xxv] One of the first examples of functionalized Grignard reagents is the Mg-halide exchange on an allylic substrate, few examples are known in literature for the Mg-halide exchange for halides attached to sp^3-hybridized carbons, see: P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320.

5.14 Experimental section

General procedures:
All reactions under a N_2 atmosphere were conducted using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere prior to use. Et_2O was distilled from Na using benzophenone as indicator under a N_2 atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under a N_2 atmosphere prior to use. Toluene was distilled from CaH_2 under a N_2 atmosphere prior to use. *t*BuOMe was distilled from CaH_2 under a N_2 atmosphere prior to use. CuBr•SMe_2 was purchased from Sigma-Aldrich. (*R*,*R*)-TaniaPhos and *(S,S)*-TaniaPhos were purchased from Sigma-Aldrich. MeMgBr was purchased from Sigma-Aldrich or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et_2O following standard procedures. Grignard reagents were titrated using *s*BuOH and small amounts of 1,10-phenanthroline before use.
Crotonic acid, N-bromosuccinimide, DCC, (3-methyloxetan-3-yl)methanol, *t*butylacetate, trifluoroacetic acid, EtSH, dichlorobenzoquinone, HG-II catalyst, imidazole, CuCN, $K_2OsO_2(OH)_4$, $(DHQ)_2AQN$, $(DHQ)_2Phal$ and $(DHQ)_2Pyr$ were purchased from Sigma-Aldrich. Azobis(isobutyronitrile) was purchased from Janssen Chimica. BnOH, H_2O_2 and $K_3Fe(CN)_6$ were purchased from Merck. DMAP, piperidine, hydrazine hydrate, TBDPSCl and methanesulfonamide were purchased from ACROS. *Iso* propyl alcohol was purchased from Labscan. Benzyl amine was purchased from Fluka. K_2CO_3 was purchased from Boom.
Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F_{254} silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by chiral GC (HP6890, Chiraldex-B-PM 30 m x 0.25 mm x 0.25 μm; HP6890, Chiralsil-DEX-CB 25 m x 0.25 mm x 0.25 μm) using flame ionization detection or HPLC analysis (chiralcel AS-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 205 nm; chiralcel OB-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 205 nm; chiralcel OJ-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 205 nm) in comparison to authentic samples of racemates of the products. Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ= 7.26 for hydrogen atoms, δ= 77.23 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a FTMS Orbitrap FischerScientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA).
For spectra see supporting information of the paper mentioned on page 143.

Bromination of crotonic acid:[55]
In a roundbottom flask equipped with stirring bar, crotonic acid (20 g, 0.23 mol, 1.0 equiv) and N-bromosuccinimide (46 g, 0.25 mol, 1.1 equiv) were dissolved in benzene (200 mL). After the solution was heated to reflux, azobis(isobutyronitile) (1.14 g, 6.97 mmol, 3 mol%) was added and the reaction mixture was kept at reflux temperature for 2 h. Then the solution was cooled to 0 °C and filtered over celite. The residue was washed with toluene (50 mL). The filtrate was concentrated and recrystallized from toluene and afforded 4-bromocrotonic acid as a white solid in several batches.

E-4-bromobut-2-enoic acid (4-bromocrotonic acid) (**5.60**):
[70% yield, white solid, mp: 74.7-75.3 °C].

^{1}H NMR δ 11.63 (s, br, 1H), 7.10 (dt, *J*= 7.3 Hz, 15.3 Hz, 1H), 6.03 (d, *J*= 15.4 Hz, 1H), 4.01 (d, *J*= 7.3 Hz, 2H), spectrum contains traces of crotonic acid; ^{13}C NMR δ 171.3 (C), 144.65 (CH), 123.99 (CH), 28.86 (CH_2); MS *m/z* 166 (M^+[^{81}Br], 56), 164 (M^+[^{79}Br], 56), 85 (M-Br, 100); HRMS calcd. for $C_4H_5{}^{79}BrO_2$ 163.9473, found 163.9471.

Bromination of tiglic acid:[26]
The procedure described in ref 26 was followed. 50 mmol scale, 15% unoptimized yield, recrystallization from Et_2O (dissolve in) and pentane.
E-4-bromo-2-methylbut-2-enoic acid (4-bromotiglic acid) (**5.62**); data in accordance with data described in ref 26.

Chlorination of vinylacetic acid:[27]
The procedure described in ref 27 was followed. 40 mmol scale, omitting mol sieves, 75% yield, instead of column chromatography the product was recrystallized from Et_2O:pentane 1:4.
E-4-chlorobut-2-enoic acid (4-chlorocrotonic acid) (**5.64**); data in accordance with data described in ref 27.

General procedure for the esterification of 4-bromocrotonic acid:
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid (1.0 equiv), BnOH (1.1 equiv) and DMAP (0.1 equiv) were dissolved in CH_2Cl_2 (5 mL/ mmol 4-bromocrotonic acid), the solution was cooled to 0 °C and DCC (1.05 equiv) was added. After addition the reaction mixture was stirred for 16 h at rt (real reaction time <4H). The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were dried and concentrated to a colorless oil. The product was purified by flash column chromatography (Et_2O:pentane 1:50) and subsequent recrystallization from pentane.
[10 mmol scale, 66% yield, white solid]

E-benzyl 4-bromobut-2-enoate (**5.65a**) data in accordance with data described in ref 56. MS *m/z* 256 (M^+[^{81}Br], 1), 254 (M^+[^{79}Br], 1), 175 (M-Br, 29), 156 (44), 107 (BnO, 28), 91 (Bn, 100).

E-benzyl 4-bromo-2-methylbut-2-enoate (**5.65c**) was prepared according to the general procedure for the esterification of 4-bromocrotonic acid.
Purified by flash chromatography (Et_2O:pentane 1:50).
[6 mmol scale, 19% unoptimized yield, colorless oil]
^{1}H NMR δ 7.42-7.28 (m, 5H), 7.01-6.92 (m, 1H), 5.20 (s, 2H), 4.01 (d, *J*= 8.5 Hz, 2H), 2.00-1.88 (m, 3H); ^{13}C NMR δ 167.05 (C), 135.97 (C), 135.48 (CH), 132.08 (C), 128.69 (CH), 128.37 (CH), 128.27 (CH), 66.88 (CH_2), 26.08 (CH_2), 12.37 (CH_3); MS *m/z* 270 (M^+[^{81}Br], 1), 268 (M^+[^{79}Br], 1), 171 (21), 91 (Bn, 100), 82 (M^+-Br-OBn, 15); HRMS calcd. for $C_{12}H_{13}{}^{81}BrO_2$ 292.9971, found 292.9973; calcd. for $C_{12}H_{13}{}^{79}BrO_2Na$ 290.9991, found 290.9994.

E-benzyl 4-chlorobut-2-enoate (**5.65b**) was prepared according to the general procedure for the esterification of 4-bromocrotonic acid.
Purified by flash chromatography (Et_2O:pentane 1:50).
[10 mmol scale, ~60% yield, colorless oil]
^{1}H NMR δ 7.44-7.31 (m, *J*= 4.6 Hz, 2.8 Hz, 5H), 7.03 (dtd, *J*= 15.4 Hz, 6.0 Hz, 1.5 Hz, 1H), 6.22-6.13 (m, 1H), 5.22 (d, *J*= 1.1 Hz, 2H), 4.15 (dt, *J*= 6.0 Hz, 1.6 Hz, 2H); ^{13}C NMR δ 165.46 (C), 142.40 (CH), 135.80 (C), 128.70 (CH), 128.43(CH), 123.82 (CH), 66.62 (CH_2), 42.58(CH_2); MS *m/z* 210 (M^+, 2), 103 (M^+-OBn, 52), 91 (Bn, 100), 68 (M^+-Cl-OBn, 32); HRMS calcd. for $C_{11}H_{11}ClO_2Na$ 233.0340, found 233.0342.

E-iso propyl 4-bromobut-2-enoate (**5.65d**) was prepared according to the general procedure for the esterification of 4-bromocrotonic acid.
Purified by flash chromatography (Et_2O:pentane 1:50).

[10 mmol scale, 70% yield, colorless oil]
^{1}H NMR δ 6.92 (dtd, *J*= 15.3 Hz, 7.4 Hz, 1.1 Hz, 1H), 5.95 (ddd, *J*= 15.3 Hz, 2.4 Hz, 1.2 Hz, 1H), 5.01 (d septet, *J*= 6.3 Hz, 1.0 Hz, 1H), 3.96 (ddd, *J*= 7.4 Hz, 1.4 Hz, 0.8 Hz, 2H), 1.21 (dd, *J*= 6.3 Hz, 1.1 Hz, 6H); ^{13}C NMR δ 165.10 (C), 141.44 (CH), 125.27(CH), 68.30 (d, CH), 29.38 (CH_2), 21.94 (CH_3); MS *m/z* 193 (M^+[^{81}Br]-Me, 1), 191 (M^+[^{79}Br]-Me, 1), 167 (M^+[^{81}Br]-*i*Pr, 67), 165 (M^+[^{79}Br]-*i*Pr, 67), 149 (M^+[^{81}Br]-O*i*Pr, 97), 147 (M^+[^{79}Br]-O*i*Pr, 100), 68 (M-Br-O*i*Pr, 52); HRMS calcd. for $C_7H_{12}{}^{81}BrO_2$ 208.9995, found 208.9992, calcd. for $C_7H_{12}{}^{79}BrO_2$ 207.0025, found 207.0013.

Thioesterification of 4-bromocrotonic acid:[57]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid (3.47 g, 21.0 mmol), EtSH (1.55 mL, 21.0 mmol) and DMAP (0.26 g, 2.10 mmol) were dissolved in CH_2Cl_2 (120 mL), the solution was cooled to 0 °C and DCC (4.76 g, 23.1 mmol) was added. After addition the reaction mixture was stirred for 16 h at rt. The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were washed with, subsequently, an aq $NaHCO_3$ solution (saturated, 150 mL), H_2O (150 mL) and a saturated brine solution (100 mL), dried and concentrated to a colorless oil. Flash chromatography (Et_2O:pentane 1:99) afforded **5.65e** as a colorless oil in 70% yield.

E-S-ethyl 4-bromobut-2-enethioate (**5.65e**) data in accordance with data described in ref 57.

General procedure for amide formation from 4-bromocrotonic acid:
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid **5.60** (1.0 equiv), the amine (1.1 equiv) and DMAP (0.1 equiv) were dissolved in CH_2Cl_2 (5 mL/mmol **5.60**), the solution was cooled to 0 °C and EDC (1.05 equiv) was added. After addition the reaction mixture was stirred for 16 h at rt. The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were dried and concentrated to a colorless oil. Flash chromatography followed by multiple recrystallizations from CH_2Cl_2 or Et_2O provided the product in unoptimized low yields (10-30%).

E-N-benzyl-4-bromobut-2-enamide (**5.65f**).
[white solid; mp: 108.3-108.5 °C]
^{1}H NMR δ 7.37-7.09 (m, 5H), 6.91-6.75 (m, 1H), 6.23 (s, br, 1H), 6.07 (dd, *J*= 14.9 Hz, 1.3 Hz, 1H), 4.43 (d, *J*= 5.6 Hz, 2H), 4.09 (d, *J*= 5.8 Hz, 2H); peaks for the cis-conformer of the amide 5.99 (d, *J*= 15.2 Hz, 1H), 3.93 (d, *J*= 7.2 Hz, 2H); ^{13}C NMR δ 164.90 (C), 138.21 (CH), 138.08 (C), 128.85, (CH) 127.93 (CH), 127.70 (CH), 126.28 (CH), 43.82 (CH_2), 43.03 (CH_2); MS *m/z* 173 (M^+-Br-H, 36), 106 (NHBn, 100), 91 (Bn, 77), 69 (C_4H_5O, 34); HRMS calcd. for $C_{11}H_{13}{}^{81}BrNO$ 256.0155, found 256.0155; calcd. for $C_{11}H_{13}{}^{79}BrNO$ 254.1076, found 254.1075.

E-4-bromo-1-(piperidin-1-yl)but-2-en-1-one (**5.65g**) was prepared according to the general procedure for amide formation from 4-bromocrotonic acid.
E-4-bromo-1-(piperidin-1-yl)but-2-en-1-one (**5.65g**); data in accordance with data described in ref 58.
[white solid]

Synthesis of *E-tert* butyl 4-bromobut-2-enoate (**5.65h**):
In a dried roundbottom flask with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid (4.84 g, 29.5 mmol) was dissolved in 150 mL of anhydrous CH_2Cl_2. *Tert* butylacetate (40 mL, 295 mmol, 10 equiv) and triflic acid (0.262 mL, 2.95 mmol, 0.1 equiv) were added. The mixture was stirred for 1 h, then diluted with CH_2Cl_2 (50 mL) and washed with a saturated aq $NaHCO_3$ solution (3 x 100 mL). The organic layer was dried and concentrated and purification with flash column chromatography (Et_2O:pentane 1:50) gave the product as colorless oil in 83% yield.

E-tert butyl 4-bromobut-2-enoate (**5.65h**); data in accordance with data described in ref 59.

MS *m/z* 207 (M^+[^{81}Br]-Me, 1), 205 (M^+[^{79}Br]-Me, 1), 149 (M^+[^{81}Br]-O*t*Bu, 43), 147 (M^+[^{79}Br]-O*t*Bu, 43), 57 (C_2HO_2, 100); HRMS calcd. for $C_8H_{13}{}^{81}BrO_2Na$ 244.9970, found 244.9967, calcd. for $C_8H_{13}{}^{79}BrO_2Na$ 243.0003, found 242.9988.

Synthesis of *E-tert* butyldimethylsilyl 4-bromobut-2-enoate:
In a dried two necked roundbottom flask equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv), imidazole (1.0 equiv) and DMAP (0.1 equiv) were dissolved in anhydrous CH_2Cl_2 (1.5 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and TBDMSCl (1.1 equiv) was added. After stirring for 16 h (0 °C to rt) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract were dried and concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:10 to 1:4) provided a mixture of the product and an unidentified side-product as a colorless oil. This mixture was used directly for AAA.

E-tert butyldimethylsilyl 4-bromobut-2-enoate (**5.65i**):
[5 mmol scale, colorless oil, ~20% yield]
^{1}H NMR δ 6.94-6.81 (m, 1H), 5.95 (ddd, *J*= 15.2 Hz, 2.6 Hz, 1.3 Hz, 1H), 3.96 (dt, *J*= 7.4 Hz, 1.4 Hz, 4H), 0.91 (s, 9H), 0.24 (s, 6H); Residual peaks side-product: 6.94-6.81 (m, 0.5H), 6.02 (dt, *J*= 15.2 Hz, 1.6 Hz, 0.5H), 4.11 (dt, *J*= 6.2 Hz, 1.5 Hz, 1H), 0.91 (s, 4.5H), 0.24 (s, 3H); ^{13}C NMR δ 165.33 (C), 142.10 (CH), 126.38 (CH), 29.12 (CH_2), 25.60 (CH_3), −4.81 (CH_3); Residual peaks side-product: 125.85 (CH), 42.42 (CH_2), 17.69 (CH_2).

E-(3-methyloxetan-3-yl)methyl 4-bromobut-2-enoate (**5.66**) was prepared according to the general procedure for the esterification of 4-bromocrotonic acid.
Purified by flash chromatography (Et_2O:pentane 1:50).
[10 mmol scale, 76% yield, colorless oil]
^{1}H NMR δ 7.01-6.88 (m, 1H), 6.00 (dd, *J*= 15.4 Hz, 1.3 Hz, 1H), 4.44 (d, *J*= 6.0 Hz, 2H), 4.30 (d, *J*= 6.0 Hz, 2H), 4.16 (s, 2H), 3.98-3.87 (m, 2H), 1.27 (s, 3H); ^{13}C NMR δ 165.39 (C), 142.42 (CH), 124.05 (CH, d, *J*= 5.6 Hz), 79.41 (CH_2), 68.86 (CH_2, t, *J*= 4.1 Hz), 39.06 (CH_2), 29.06 (CH_2, t, *J*= 5.8 Hz), 21.13 (CH_3, s); MS *m/z* 167 (M^+[^{81}Br], 3), 165 (M^+[^{79}Br], 5), 149 (M^+[^{81}Br]-OR, 100), 147 (M^+[^{79}Br]-OR, 100), 68 (M-Br-OR, 47), 55 (C_3H_3O, 45); HRMS calcd. for $C_9H_{15}{}^{81}BrO_3$ 251.0106, found 251.0097.

General procedure for the asymmetric allylic alkylation with MeMgBr:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuBr•SMe_2 (1.0 mol%) and (*R*,*R*)-TaniaPhos (1.1 mol%) were dissolved in anhydrous CH_2Cl_2 (4.0 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to −78 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 1.2 equiv) was added. After stirring for an additional 10 min, a solution of substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 1.0 mL/mmol substrate) was added with syringe pump over 0.5 h. The reaction mixture was stirred for 16 h at −78 °C and subsequently EtOH (0.4 mL/mmol substrate) and an aq NH_4Cl-solution (1 M, 2.0 mL/mmol substrate) were added. The mixture was warmed to rt and an additional 10 mL/mmol substrate of the NH_4Cl-solution and 10 mL/mmol substrate of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:99) afforded the product as a colorless oil.
(*S*)-benzyl 2-methylbut-3-enoate (**5.67a**):
[colorless oil; 10 mmol scale, 89% yield, 96% *ee*; 6.6 mmol scale, 90% yield, 98% *ee*; 4 mmol scale, 88% yield, 98% *ee*; 2.5 mmol scale, 88% yield, 98% *ee*; 0.5 mmol scale, 86% yield, 99% *ee*]; *R*-enantiomer: 2.0 mmol scale, 81% yield, 96% *ee*.
$[\alpha]_D^{20}$= +19.0 (c= 1.0, CH_2Cl_2), *S*-enantiomer; using (*S*,*S*)-TaniaPhos $[\alpha]_D^{20}$= −20.2 (c= 1.0, CH_2Cl_2), *R*-enantiomer; literature[38f] value for 10% *ee* $[\alpha]_D^{20}$= −1.5 (c= 0.7, CH_2Cl_2), *R*-enantiomer.

^{1}H NMR δ 7.38-7.25 (m, 5H), 5.92 (ddd, *J*= 17.5 Hz, 10.2 Hz, 7.5 Hz, 1H), 5.17-5.04 (m, 4H), 3.23-3.13 (m, 1H), 1.26 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR δ 174.41 (C), 137.17 (CH), 136.19 (C), 128.70 (CH), 128.32 (CH), 128.17 (CH), 116.24 (CH_2), 66.50 (CH_2), 43.85 (CH), 16.86 (CH_3); MS *m/z* 190 (M^+, 1), 91 (Bn, 100); HRMS calcd. for $C_{12}H_{15}O_2$ 191.1067, found 191.1067; *Ee* was determined by chiral HPLC analysis, column: Chiralcel-OB-H, 98:2 heptane:*i*PrOH, retention times (min): 11.2 (*R*-enantiomer), 11.6 (*S*-enantiomer); traces of S_N2 product (<5%) were found using NMR.

Asymmetric allylic alkylation of **5.65a** with EtMgBr:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuBr•SMe_2 (5.0 mol%) and TaniaPhos (5.25 mol%) were dissolved in anhydrous CH_2Cl_2 (4.0 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to −78 °C and a solution of substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 1.0 mL/mmol substrate) was added. After stirring for an additional 10 min, EtMgBr (Aldrich, 3.0 M solution in Et_2O, 1.2 equiv) was added dropwise. The reaction mixture was stirred overnight at −78 °C and subsequently EtOH (0.4 mL/mmol substrate) and an aq NH_4Cl-solution (1 M, 2.0 mL/mmol substrate) were added. The mixture was warmed to rt and an additional 5 mL of the aq NH_4Cl-solution and 5 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. This oil was analyzed by ^{1}H-NMR and GC-MS.

E-benzyl crotonate (**5.70**)
MS *m/z* 176 (M^+, 5), 91 (Bn, 100).

S_N2' product: benzyl 2-ethylbut-3-enoate (**5.67a**)
MS *m/z* 204 (M^+, 1), 91 (Bn, 100).

S_N2 product: *E*-benzyl hex-2-enoate (**5.68a**)
MS *m/z* 204 (M^+, 5), 97 (M^+-OBn, 67), 91 (Bn, 100), 55 (C_3H_3O, 32).

1,4-addition product: benzyl 2-ethylcyclopropanecarboxylate (**5.69a**)
MS *m/z* 204 (M^+, 3), 97 (M^+-OBn, 28), 91 (Bn, 100), 55 (C_3H_3O, 17).

S_N2 + 1,4-addition product: benzyl 3-ethylhexanoate (**5.71a**)
MS *m/z* 234 (M^+, 1), 108 (19), 92 (22), 91 (Bn, 100), 83 (19).

General procedure for the olefin reduction of terminal β,γ-unsaturated esters: [34]
In a roundbottom flask equipped with stirring bar under an O_2 atmosphere the substrate (1 equiv) was dissolved in EtOH (6 mL/mmol substrate). A solution of catalyst **5.80**[34] (20 mol%) in EtOH (1.4 mL/mmol substrate) and hydrazine hydrate (10 equiv) in EtOH (to match with the amount of catalyst solution) was added with syringe pump over 1 h under vigorously stirring and the reaction was vigorously stirred for another 1 h. Subsequently the reaction mixture was extracted with pentane (4 x 10 mL/mmol substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 3:97) afforded the product.

(*S*)-benzyl 2-methylbutanoate (**5.67a**) data in accordance with data described in ref 60.
[colorless oil, 0.5 mmol scale, 91% yield, >95% *ee*]
HRMS calcd. for $C_{12}H_{16}O_2Na$ 215.1048, found 215.1038.
$[\alpha]_D^{20}$= +10.0 (c= 1.0, $CHCl_3$), *S*-enantiomer; literature[61] value for 1.7% *ee* $[\alpha]_D^{20}$= +0.20 (c= 1.87, $CHCl_3$), *S*-enantiomer. *Ee* was determined by chiral HPLC analysis, column: Chiralcel-OB-H, 99:1 heptane:*i*PrOH, retention times (min): 10.6 (*R*-enantiomer), 10.9 (*S*-enantiomer).

General procedure for the deprotection of benzyl esters:
In a dried Schlenk equipped with stirring bar and septum under a N_2 atmosphere the substrate was dissolved in anhydrous CH_2Cl_2 (3 mL/mmol substrate). Then the solution was cooled to −78 °C and BBr_3 (1.0 M solution in CH_2Cl_2, Aldrich, 1.5 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C and was then transferred to an ice bath (0 °C). After additional stirring for 1.5 h the reaction was quenched by careful addition of ice at 0 °C followed by water (2.0 mL/mmol substrate). The aqueous layer was acidified by addition of a saturated aqueous solution of $KHSO_4$ (5 mL/mmol substrate) and the aqueous layer was extracted with CH_2Cl_2 (3x 5 mL/mmol substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography afforded the product.

[colorless oil, 1.0 mmol scale, 85% yield, 94% *ee*]
(*S*)-2-methylbut-3-enoic acid (**5.82**) data in accordance with data described in ref 62.
Purified by flash column chromatography (Et_2O:pentane 1:10).
$[\alpha]_D^{20}$= +32.1 (c= 1.0, CH_2Cl_2)
Ee was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 °C to 90°C in 4 min, 90 °C for 40 min, 90 °C to 160°C in 7 min, retention times (min): 46.7 (*R*-enantiomer), 48.0 (*S*-enantiomer), 48.7 (isomerized product).

General procedure for the hydroboration, followed by oxidation of β,γ-unsaturated esters:[63]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv) was dissolved in anhydrous THF (1 mL/mmol substrate) and cooled to 0 °C and 9-BBN-THF (Aldrich, 0.5 M solution in THF, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 1.5 h at rt and subsequently EtOH (3.5 equiv) was added to destroy the excess of 9-BBN. Subsequently a pH 7 potassium phosphate buffer (4 mL/mmol substrate) and H_2O_2 (30% solution in H_2O, 4 mL/mmol substrate, ~4.7 equiv) were added dropwise at 0 °C. The reaction mixture was then allowed to warm up to rt and stirred for 1 h. Then the remaining peroxide was quenched at 0 °C by slow addition of an saturated aq solution of $NaHSO_3$ (10 mL/ mmol substrate) at 0 °C. The layers were separated and the aqueous layer was washed with Et_2O (3x 20 mL/ mmol substrate). The combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O:pentane 1:4) afforded the product as a colorless oil.

(*S*)-benzyl 4-hydroxy-2-methylbutanoate (**5.83**):
[0.5 mmol scale, 81% yield, 98% *ee*]
^{1}H NMR δ 8.59 (s, br, 1H), 7.39-7.25 (m, 5H), 5.10 (s, 2H), 3.64 (ddd, *J*= 6.3 Hz, 4.2 Hz, 1.8 Hz, 2H), 2.73 – 2.62 (m, 1H), 1.99-1.88 (m, 1H), 1.74-1.63 (m, 1H), 1.19 (dd, *J*= 7.1 Hz, 1.3 Hz, 3H); ^{13}C NMR δ 176.91 (C), 136.13 (C), 128.71 (CH), 128.36 (CH), 128.23 (CH), 66.47 (CH_2), 60.61 (CH_2), 36.65 (CH), 36.39 (CH_2), 17.27 (CH_3); MS *m/z* 207 ($M-H^+$, 1), 91 (Bn, 100); HRMS calcd. for $C_{12}H_{16}O_3Na$ 231.0992, found 231.0986.
$[\alpha]_D^{20}$= +11.7 (c= 1.0, CH_2Cl_2). *Ee* was determined by chiral HPLC analysis, column: Chiralcel-AS-H, 95:5 heptane:*i*PrOH, retention times (min): 14.6 (*R*-enantiomer), 15.8 (*S*-enantiomer).

General procedure for the cross metathesis of β,γ-unsaturated esters:[64]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere the corresponding catalyst (5.0 mol%) and dichlorobenzoquinone (10 mol%) were dissolved in anhydrous CH_2Cl_2 (4.0 mL/mmol substrate). After stirring for 2 min a mixture of both the substrate (1.0 equiv) and the terminal alkene (1.2-2.0 equiv) were added. Then a reflux condenser under a N_2 atmosphere was placed on the Schlenk tube and the mixture was refluxed for the indicated time. Then the reaction

mixture was quenched with ethyl vinyl ether (1.0 mL/mmol substrate) and stirred for 10 min. Subsequently the reaction mixture was concentrated to a yellow oil. Flash column chromatography afforded the product.

(*S*,*E*)-benzyl 2-methyldec-3-enoate (**5.58a**):
Purified by flash chromatography (Et_2O:pentane gradient 1:100 to 1:50).
[colorless oil, 3.0 mmol scale, 8 h reaction time, 84% yield; 1.0 mmol scale, 8 h reaction time, 74% yield]
$[\alpha]_D^{20}$= +33.8 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.37-7.28 (m, 5H), 5.58-5.44 (m, 2H), 5.11 (s, 2H), 3.18-3.09 (m, 1H), 2.03-1.94 (m, 2H), 1.34-1.21 (m, 11H), 0.87 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 175.11 (C), 136.37 (C), 132.75 (CH), 128.74 (CH), 128.69 (CH), 128.27 (CH), 128.12 (CH), 66.34 (CH_2), 43.08 (CH), 32.62 (CH_2), 31.89 (CH_2), 29.35 (CH_2), 28.97 (CH_2), 22.81 (CH_2), 17.64 (CH_3), 14.30 (CH_3); MS *m/z* 274 (M^+, 1), 91 (Bn, 100), 83 (C_5H_7O, 33), 55 (C_3H_3O, 38); HRMS calcd. for $C_{18}H_{26}O_2Na$ 297.1831, found 297.1822.

(*S*,*E*)-benzyl 8-(*tert*-butyldiphenylsilyloxy)-2-methyloct-3-enoate (**5.58c**):
Purified by flash chromatography (Et_2O:pentane 1:50).
[colorless oil, 0.5 mmol scale, 8 h reaction time, 66% yield]
$[\alpha]_D^{20}$= +17.6 (c= 1.0, CH_2Cl_2); ^{1}H NMR δ 7.66 (dd, *J*= 7.8 Hz, 1.6 Hz, 4H), 7.45-7.25 (m, 11H), 5.58-5.44 (m, 2H), 5.11 (s, 2H), 3.68-3.60 (m, 2H), 3.20-3.09 (m, 1H), 1.99 (dd, *J*= 12.5 Hz, 7.2 Hz, 2H), 1.58-1.50 (m, 2H), 1.48-1.37 (m, 2H), 1.25 (dd, *J*= 7.0 Hz, 1.1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR δ 175.06 (C), 136.34 (C), 135.77 (CH), 134.28 (C), 132.48 (CH), 129.72 (CH), 129.00 (CH), 128.70 (CH), 128.28 (CH), 128.16 (CH), 127.79 (CH), 66.37 (CH_2), 63.94 (CH_2), 43.07 (CH), 32.29 (CH_2), 32.17 (CH_2), 27.08 (CH_3), 25.60 (CH_2), 19.43 (C), 17.65 (CH_3); MS *m/z* 405 (1), 207 ($C_{11}H_{15}O_2Si$, 75), 91 (Bn, 100), 78 (C_6H_6, 29); HRMS calcd. for $C_{32}H_{40}O_3SiNa$ 523.2644, found 523.2622.

(*S*,*E*)-benzyl 5-bromo-2-methylpent-3-enoate (**5.58d**):
Purified by flash chromatography (Et_2O:pentane gradient 1:200 to 1:50).
[colorless oil,[xxvi] 2.5 mmol scale, 24 h reaction time, 1,4-dibromobutene was used as alkene, 73% yield, 96% *ee*]
^{1}H NMR δ 7.40-7.27 (m, 5H), 5.92-5.73 (m, 2H), 5.12 (s, 2H), 3.92 (dd, *J*= 7.2 Hz, 0.6 Hz, 2H), 3.27-3.17 (m, 1H), 1.29 (d, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 173.91 (C), 135.98 (C), 134.06 (CH), 128.74 (CH), 128.40 (CH), 128.19 (CH), 128.10 (CH), 66.69 (CH_2, t, *J* 6.4), 42.43 (CH), 32.38 (CH_2), 17.06 (CH_3); MS *m/z* 284 (M^+[^{81}Br), 1), 282 (M^+[^{79}Br], 1), 91 (Bn, 100); HRMS calcd. for $C_{13}H_{15}{}^{79}BrO_2Na$ 305.0153, found 305.0144.
$[\alpha]_D^{20}$= +26.1 (c= 1.0, CH_2Cl_2). *Ee* was determined by chiral HPLC analysis, column: Chiralcel-OJ-H, 99:1 heptane:*i*PrOH, retention times (min): 31.2 ((*R*)-enantiomer), 33.5 ((*S*)-enantiomer).

Synthesis of *tert*-butyl(hex-5-enyloxy)diphenylsilane:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv) and TBDPSCl (1.1 equiv) were dissolved in anhydrous THF (5 mL/mmol substrate) at rt. The solution was cooled to 0 °C and imidazole (1 equiv) was added. The cloudy mixture was stirred for 16 h. Then the reaction was quenched with an aqueous HCl solution (4 M, 5 mL/mmol substrate). Et_2O (20 mL/mmol substrate) was added, and the aqueous layer was extracted with Et_2O (1x 20 mL/mmol substrate). Then the combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL/mmol substrate) and brine (20 mL/mmol substrate). The combined organic layers were dried and carefully concentrated to a yellow oil. Flash column chromatography afforded the product as a colorless oil (Et_2O:pentane 1:20).

tert-butyl(hex-5-enyloxy)diphenylsilane:
[1.5 mmol scale, 81% yield]
^{1}H NMR δ 7.83-7.77 (m, 4H), 7.63-7.32 (m, 6H), 5.90 (ddt, *J*= 16.9 Hz, 10.2 Hz, 6.6 Hz, 1H), 5.19-4.94 (m, 2H), 3.79 (t, *J*= 6.3 Hz, 2H), 2.22-2.07 (m, 2H), 1.76-1.53 (m, 4H), 1.18 (s, 9H); ^{13}C NMR δ 139.06 (CH), 135.78 (CH), 134.29 (C), 129.73 (CH), 127.81 (CH), 114.62 (CH_2), 63.97 (CH_2),

[xxvi] Occasionaly the product was polluted with 2,6-dichlorobenzoquinone, in these cases a yellow oil was obtained.

33.70 (CH_3), 32.24 (CH_3), 27.11 (CH_2), 25.35 (CH_3), 19.45 (CH_3); MS *m/z* 281 (M^+-*t*Bu, 74), 199 ($C_{12}H_{11}OSi$, 100), 183 ($C_{12}H_{11}Si$, 43); HRMS calcd. for $C_{22}H_{31}OSi$ 339.2144, found 339.2136.

General procedure for the reduction of internal β,γ-unsaturated esters:
In a roundbottom flask equipped with stirring bar under an O_2 atmosphere the substrate (1 equiv) was dissolved in EtOH (8 mL/mmol substrate). A solution of catalyst **5.80**[34] (1 equiv) in EtOH (8 mL/mmol substrate) and hydrazine hydrate (50 equiv) in EtOH (to match with the amount of catalyst solution) was added by syringe pump over 6 h under vigorously stirring and the reaction was vigorously stirred for another 1 h. During the reaction the flask was occasionally purged with O_2 (2x everyH) to remove the formed N_2-gas. Subsequently the reaction mixture was extracted with pentane (4x 10 mL/mmol substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et_2O: pentane 3:97) afforded the product as a colorless oil.

(*S*)-benzyl 2-methyldecanoate (**5.86**):
[0.25 mmol scale, 75% yield, 89% conversion]
^{1}H NMR δ 7.41-7.29 (m, 5H), 5.12 (s, 2H), 2.53-2.45 (m, 1H), 1.73-1.60 (m, 1H), 1.48-1.36 (m, 1H), 1.36-1.19 (m, 12H), 1.16 (d, *J*= 7.0 Hz, 3H), 0.88 (t, *J*= 6.9 Hz, 3H), residual peaks from the starting material: 5.58-5.44 (2 H, m), 3.18-3.13 (m, 2H), 2.03-1.96 (m, 2H). ^{13}C NMR δ 176.90 (C), 136.43 (C), 132.70 (CH), 128.66 (CH), 128.20 (CH), 66.08 (CH_2), 39.71 (CH), 33.97 (CH_2), 32.01 (CH_2), 29.65 (CH_2), 29.59 (CH_2), 29.38 (CH_2), 27.33 (CH_2), 22.81 (CH_2), 17.20 (CH_3), 14.26 (CH_3), residual peaks from the starting material: 43.03 (CH), 32.56 (CH_2), 31.84 (CH_2), 28.92 (CH_2), 17.58 (CH_3); MS *m/z* 276 (M^+, 1), 91 (Bn, 100), 57 (C_4H_9, 20); HRMS calcd. for $C_{18}H_{28}O_2Na$ 299.1982, found 299.1976.
$[\alpha]_D^{20}$= +18.6 (c= 0.8, CH_2Cl_2, sample contains traces of (*S*,*E*)-benzyl 2-methyldec-3-enoate)

Procedure for the diastereoselective cuprate addition to 5-bromo 2-methylpent-3-enoate (**5.85d**):
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, CuCN (2.0 equiv) was dissolved in anhydrous Et_2O (4 mL/mmol substrate) and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 2.0 equiv) was added. After 5 min stirring at rt the mixture was cooled to −40 °C and anhydrous CH_2Cl_2 (4 mL/mmol substrate) was added. Then a solution of substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 2.0 mL/mmol substrate) was added by syringe pump over 2 h. The reaction mixture was stirred for 16 h at −40 °C and subsequently EtOH (0.4 mL/mmol substrate) and an aq NH_4Cl-solution (1M, 2.0 mL/mmol substrate) were added. The mixture was warmed to rt and an additional 10 mL/mmol substrate of the NH_4Cl-solution and 10 mL/mmol substrate of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O: pentane 1:99) afforded the product as a colorless oil.

(2*S*,3*S*)-benzyl 2,3-dimethylpent-4-enoate (**5.87**):
[0.25 mmol scale, 80% yield, 87:13 S_N2:S_N2']
^{1}H NMR δ 7.44-7.28 (m, 5H), 5.70-5.57 (m, 2H), 5.13 (d, *J*= 2.2 Hz, 2H), 5.06-4.98 (m, 2H), 2.53-2.33 (m, 2H), 1.12 (d, *J*= 6.9 Hz, 3H), 1.01 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 175.92 (C), 140.90 (CH), 136.25 (C), 128.64 (CH), 128.32 (CH), 128.30 (CH), 115.28 (CH_2), 66.21 (CH_2), 45.14 (CH), 41.26 (CH), 18.53 (CH_3), 14.68 (CH_3); MS *m/z* 218 (M^+, 1), 91 (Bn, 100), 55 (C_3H_3O, 20); HRMS calcd. for $C_{14}H_{18}O_2Na$ 241.1199, found 241.1196.
$[\alpha]_D^{20}$= −9.8 (c= 0.5, CH_2Cl_2, sample contains traces of (*S*,*E*)-benzyl 2-methylhex-3-enoate)

Epoxidation of (*S*)-benzyl 2-methylbut-3-enoate (**5.67a**).
The procedure described in ref 65 was followed.
60% conversion, 1:1 mixture of diastereomers, colorless oil.

General procedure for the Sharpless asymmetric *cis* dihydroxylation of β,γ-unsaturated esters:[66]
In a Schlenk tube equipped with septum and stirring bar $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $K_2OsO_2(OH)_4$ (1.0 mol%) and methanesulfonamide (1 equiv) were dissolved in H_2O (5 mL/mmol substrate). Then the corresponding ligand (2.5 mol%) was added followed by *t*BuOH (4 mL/mmol substrate). The solution was cooled to 0 °C and the substrate (1 equiv) in *t*BuOH (additional 1 mL/mmol substrate) was added dropwise. The mixture was stirred for 16 h. Then a saturated aqueous $NaHSO_3$ solution (1 mL/ mmol substrate) was slowly added and the suspension was warmed to rt with vigorous stirring. MeOAc[xxvii] (20 mL/mmol substrate) was added, and the aqueous layer was extracted with MeOAc (5x 20 mL/mmol substrate). The combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient pentane:Et_2O 1:1 to Et_2O) afforded the product as a colorless oil.

(3*S*,4*S*)-4-hydroxy-3-methyldihydrofuran-2(3H)-one ((3*S*,4*S*)-**5.92**) data in accordance with data described in ref 67.
[colorless oil, 0.5 mmol scale, 61% yield, high *ee* (see SI of ref 68 for spectra)]
$[\alpha]_D^{20}$= −67.9 (c= 1.0, $CHCl_3$); literature[44a] value for $[\alpha]_D^{20}$= +55.1 (c= 2.0, $CHCl_3$), (3*R*,4*R*)-enantiomer. *Ee* was determined by chiral GC analysis, column: Chiraldex-G-TA, 50 °C to 105°C in 5.5 min; 105 °C for 120 min, 105 °C to 170°C for 32.5 min; retention times (min): 127.7 ((*R*,*R*)-enantiomer), 131.3 ((*S*,*S*)-enantiomer).

(3*R*,4*S*)-4-hydroxy-3-methyldihydrofuran-2(3H)-one ((3*R*,4*S*)-**5.92**) data in accordance with data described in ref 69.
[colorless oil, 0.5 mmol scale, 46% yield, 98% *ee*]
$[\alpha]_D^{20}$= −52.0 (c= 0.5, $CHCl_3$, sample contains traces of methanesulfonamide); literature[44a] value for $[\alpha]_D^{20}$= +6.82 (c= 2.2, $CHCl_3$), (3*S*,4*R*)-enantiomer. *Ee* was determined by chiral GC analysis, column: Chiraldex-G-TA, 50 °C to 130°C in 8 min, 130 °C for 40 min, 130 °C to 170°C in 20 min; retention times (min): 50.0 ((*S*,*R*)-enantiomer), 54.0 ((*R*,*S*)-enantiomer).

General procedure for the iodolactonization of β,γ-unsaturated esters with a terminal olefin towards 5-membered lactones:
In a Schlenk tube equipped with stirring bar and septum under a N_2 atmosphere, bispyridine iodonium tetrafluoroborate (1.1 equiv) was dissolved in CH_2Cl_2 (20 mL/mmol substrate). The reaction was cooled to −78 °C and HBF_4 (54% in Et_2O, 1.5 equiv) was added, the solution turns pink. Then the substrate dissolved in CH_2Cl_2 (10mL/mmol substrate) was added slowly. After stirring for 1.5 h (−78 °C to −10 °C) the reaction was quenched with an aq $Na_2S_2O_3$ solution (20 mL/mmol substrate) and extracted by CH_2Cl_2 (2x 10 mL/mmol substrate). Then the combined organic extracts were washed with water (2x 10 mL/mmol substrate) dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et_2O:pentane 1:49 to 2:23) afforded the product.

(3*R*,4*S*)-4-iodo-3-methyldihydrofuran-2(3H)-one (**5.93**):
[colorless oil, 0.25 mmol scale, 27% yield, 96% *ee*]
^{1}H NMR δ 4.61 (dd, *J*= 9.4 Hz, 7.3 Hz, 1H), 4.38 (dd, *J*= 10.0 Hz, 9.4 Hz, 1H), 4.05-3.95 (m, 1H), 2.73 (dq, *J*= 10.8 Hz, 7.1 Hz, 1H), 1.34 (d, *J*= 7.1 Hz, 3H); ^{13}C NMR δ 176.00 (C), 73.97 (CH), 45.56 (CH_2), 17.40 (CH), 12.59 (CH_3); MS *m/z* 226 (M^+, 14), 127 (I^+, 19), 99 (M^+-I, 32), 71 ($C_3H_3O_2$, 26), 55 (C_3H_3O, 100); HRMS calcd. for $C_5H_8IO_2$ 226.9563, found 226.9562.
$[\alpha]_D^{20}$= −16.9 (c= 1.0, CH_2Cl_2). *Ee* was determined by chiral GC analysis, column: Chiralsil DEX-CB, 50 °C for 5 min, 50 °C to 80°C in 6 min, 80 °C for 20 min, 80 °C to 180°C in 20 min; retention times (min): 44.8 (*R*,*S*-enantiomer), 45.0 (*S*,*R*-enantiomer).

[xxvii] MeOAc was chosen as extraction solvent due to its high polarity, since the products are highly water soluble.

General procedure for the iodolactonization of β,γ-unsaturated esters with a terminal olefin towards 4-membered lactones:
In a Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, I_2 (5 equiv) and K_3PO_4 (5 equiv) were dissolved in anhydrous CH_2Cl_2 (100 mL/mmol substrate). Then the substrate (1 equiv) in anhydrous CH_2Cl_2 (5 mL/mmol substrate) was added dropwise. After stirring for 40 h the reaction mixture was quenched with a saturated aq $Na_2S_2O_3$ solution (50 mL/mmol substrate). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x 50 mL/mmol substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et_2O:pentane 1:49 to 2:23) afforded the product.

(3*S*,4*R*)-4-(iodomethyl)-3-methyloxetan-2-one (**5.94**):
[colorless oil, 0.25 mmol scale, 47% yield, 97% *ee*]
^{1}H NMR δ 4.40-4.26 (m, 1H), 3.54 (dd, *J*= 10.0 Hz, 4.8 Hz, 1H), 3.45-3.35 (m, 1H), 3.31 (t, *J*= 9.7 Hz, 1H), 1.47 (d, *J*= 7.5 Hz, 3H); ^{13}C NMR δ 170.11 (C), 77.13 (CH), 53.28 (CH), 12.90 (CH_3), 3.78 (CH_2); MS *m/z* 226 (M^+, 1), 127 (I^+, 15), 56 (C_3H_3O, 13), 55 (C_3H_3O, 100); HRMS calcd. for $C_5H_8IO_2$ 226.9563, found 226.9563.
$[\alpha]_D^{20}$= +19.2 (c= 1.0, CH_2Cl_2, sample contains traces of (3*R*,4*S*)-4-iodo-3-methyldihydrofuran-2(3H)-one). *Ee* was determined by chiral GC analysis, column: Chiralsil DEX-CB, 50 °C for 5 min, 50 °C to 80 °C in 6 min, 80 °C for 20 min, 80 °C to 180°C in 20 min; retention times (min): 44.3 ((*R*,*S*)-enantiomer), 44.6 ((*S*,*R*)-enantiomer), 44.8 ((*R*,*S*)-enantiomer of 5-membered lactone).

(*S*,*E*)-2-methyldec-3-enoic acid (**5.95**) was prepared *via* the general procedure for the deprotection of benzyl esters:
Purified by flash column chromatography (pentane:Et_2O 10:1).
[colorless oil, 0.3 mmol scale, 84% yield]
^{1}H NMR δ 5.74-5.41 (m, 2H), 3.19-3.07 (m, 1H), 2.02 (dd, *J*= 6.7 Hz, 2H), 1.43-1.19 (m, 11H), 0.88 (t, *J*= 6.6 Hz, 3H); ^{13}C NMR δ 181.29 (C), 133.18 (CH), 128.08 (CH), 42.81 (CH), 32.56 (CH_2), 31.82 (CH_2), 29.24 (CH_2), 28.94 (CH_2), 22.76 (CH_2), 17.43 (CH_3), 14.23 (CH_3); MS *m/z* 184 (M^+, 1), 74 (72), 69 (C_4H_5O, 98), 55 (C_3H_3O, 100); HRMS calcd. for $C_{11}H_{21}O_2$ 185.1536, found 185.1533.
$[\alpha]_D^{20}$= +42.2 (c= 1.0, CH_2Cl_2).

General procedure for the iodolactonization of β,γ-unsaturated esters with an internal olefin:
In a Schlenk tube equipped with stirring bar and septum under a N_2 atmosphere, bispyridine iodonium tetrafluoroborate (1.1 equiv) was dissolved in CH_2Cl_2 (20 mL/mmol substrate). The reaction mixture was cooled to −78 °C and HBF_4 (54% in Et_2O, 1.5 equiv) was added, the solution turns pink. Then the substrate dissolved in CH_2Cl_2 (10 mL/mmol substrate) was added slowly. After stirring for 1.5 h (−78 °C to −10 °C) the reaction was quenched with an aq $Na_2S_2O_3$ solution (20 mL/mmol substrate) and extracted by CH_2Cl_2 (2x 10 mL/mmol substrate). Then the combined organic extracts were washed with water (2x 10 mL/mmol substrate) dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et_2O:pentane 1:49 to 2:23) afforded the product.

(3*R*,4*S*,5*R*)-5-hexyl-4-iodo-3-methyldihydrofuran-2(3*H*)-one (**5.96**):
[colorless oil, 0.25 mmol scale, 65% yield]
^{1}H NMR δ 4.51 (ddd, *J*= 9.8 Hz, 8.5 Hz, 2.9 Hz, 1H), 3.60 (dd, *J*= 11.7 Hz, 9.9 Hz, 1H), 2.80 (dq, *J*= 11.8 Hz, 7.1 Hz, 1H), 2.02-1.88 (m, 1H), 1.66-1.18 (m, 12H), 0.89 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 175.42 (C), 85.93 (CH), 47.02 (CH), 32.17 (CH_2), 31.67 (CH_2), 29.00 (CH_2), 25.49 (CH_2), 25.13 (CH), 22.65 (CH_2), 14.19 (CH_3), 12.50 (CH_3); MS *m/z* 225 (M^+-hexyl, 3), 109 (C_7H_9O, 32), 109 (C_6H_9O, 33), 83 (C_5H_7O, 58), 69 (C_4H_5O, 57), 55 (C_3H_3O, 100); HRMS calcd. for $C_{11}H_{12}IO_2$ 311.0503, found 311.0501.
$[\alpha]_D^{20}$= +41.9 (c= 1.0, CH_2Cl_2)

Synthesis of racemic benzyl 2-methylbut-3-enoate (**5.67a**):
Synthesis of racemic 2-methylbut-3-enoic acid (**5.74**) was performed via the procedure described in ref 70 omitting the addition of BnBr. The crude product was used to prepare benzyl 2-methylbut-3-enoate **5.67a** *via* the general procedure for the esterification of 4-bromocrotonic acid (38% yield over 2 steps). For experimental data *vide supra*.

5.15 References and notes

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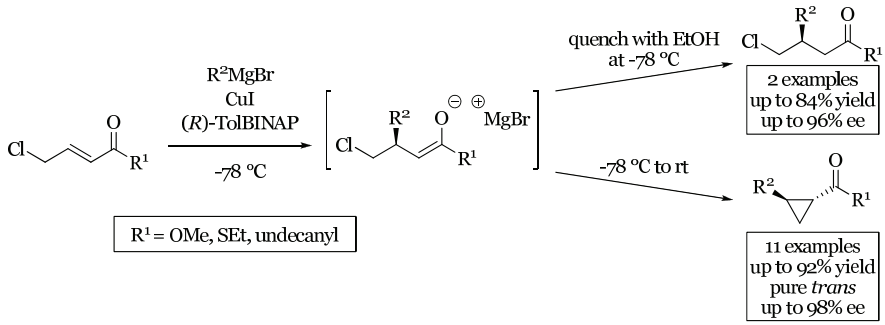
Chapter 6

Cu-Catalyzed Enantioselective Synthesis of *trans* 1-Alkyl-2-Substituted Cyclopropanes via Tandem Conjugate Addition-Intramolecular Enolate Trapping

Cu-TolBINAP catalyzed conjugate addition of Grignard reagents to 4-chloro α,β-unsaturated esters, thioesters and ketones leads to 4-chloro-3-alkylsubstituted thioesters and ketones in up to 84% yield and up to 96% ee upon protonation of the corresponding enolates at low temperature. Tandem conjugate addition-enolate trapping, however, yields trans 1-alkyl-2-substituted cyclopropanes in up to 92% yield and up to 98% ee. The versatility of this reaction is illustrated by the formal syntheses of cascarillic acid and grenadamide. Furthermore, a synthetic route to majusculoic acid, as well as an approach for the synthesis of tri-1,2,3-substituted cyclopropanes are proposed.



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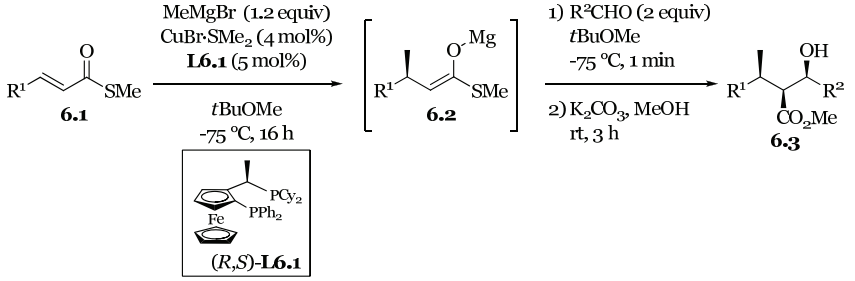
6.1 Tandem asymmetric conjugate addition-trapping reactions using Grignard reagents

Tandem reactions are attracting increasing interest in the chemical community because of their potential atom efficiency and their ability to increase structural diversity and stereochemical complexity in a stereocontrolled manner.[1] ACA-trapping reactions have been applied to the addition of zinc reagents with subsequent trapping of the zinc enolate.[2] Since Mg-enolates show different levels of reactivity, ACA of Grignard reagents and subsequent reactions of the intermediate enolate with aldehydes provides an important alternative and provides access to new synthetic building blocks with multiple stereogenic centers.

Only a single example of tandem ACA-trapping reactions with Grignard reagents is known. Feringa and co-workers reported[3] a tandem protocol for the ACA of Grignard reagents to acyclic α,β-unsaturated thioester **6.1** followed by an aldol reaction with a range of aldehydes to provide β-hydroxyesters **6.3** with high enantioselectivity (up to 95%, Table 6.1, entries 1-8) and diastereoselectivity (>96%). The ACA of MeMgBr to the cinnamyl thioesters was used primarily because of the relatively large difference in A-value[4] of the phenyl and methyl groups (3.0 vs. 1.7 kcal). For ACA to substrates that incorporate substituents with a smaller difference in A-value[i] (Me: 1.7 kcal vs. $CH_2OTBDPS$: ~1.8 kcal) a complete loss of diastereoselectivity was observed (entry 9).

The configuration of the products can be rationalized using a Zimmerman-Traxler transition state model in which the *Z*-enolate leads to *all syn*-products as is found empirically (Figure 6.1). In this model, minimization of the *syn*-pentane

Table 6.1. *Tandem ACA-aldol reaction reported by Feringa and co-workers.*



entry	R^1	R^2	yield (%)	ee (%)	de (%)
1	Ph	Ph	66	95	>96
2	Ph	pNO$_2$C$_6$H$_4$	62	95	>96
3	Ph	pBrC$_6$H$_4$	68	95	>96
4	Ph	pMeOC$_6$H$_4$	54	95	>96
5	Ph	pentyl	74	95	>96
6	Ph	cyclohexyl	76	95	>96
7	Ph	*t*Bu	73	95	>96
8	pClC$_6$H$_4$	Ph	49	99	>96
9	$CH_2OTBDPS$	Ph	49	98	~0

[i] Although unlikely the loss of diastereoselectivity by an additional coordination of the magnesium to the oxygen atom of $CH_2OTBDPS$ in the transition state cannot be excluded.

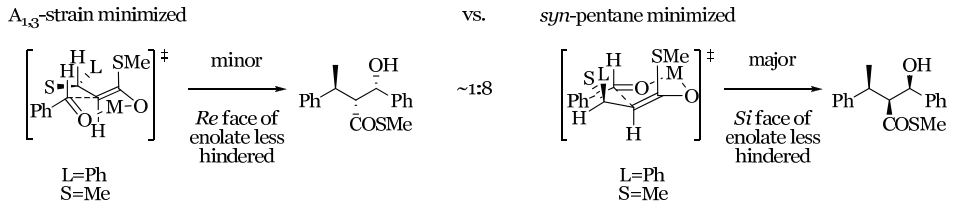
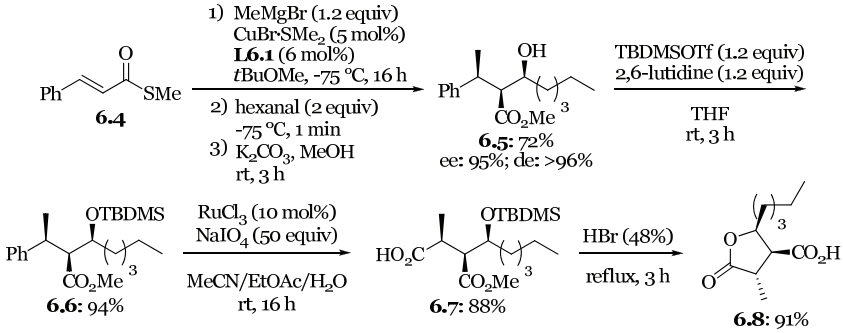


Figure 6.1. *Transitions state models for anti,syn and syn,syn selectivity.*

interactions in the enolate promotes *re*-facial attack, while minimization of the $A_{1,3}$-strain in the enolate would promote *si*-facial attack leading to the minor diastereoisomer.

The synthetic potential of this approach to tandem catalysis was illustrated through the total synthesis of phaseolinic acid (**6.8**), which was achieved in 4 steps (54% overall yield, 95% ee, >90% de, Scheme 6.1). To further expand the scope of tandem ACA-enolate trapping reactions, the synthesis of cyclopropanes via ACA-intramolecular enolate trapping is explored in this chapter.

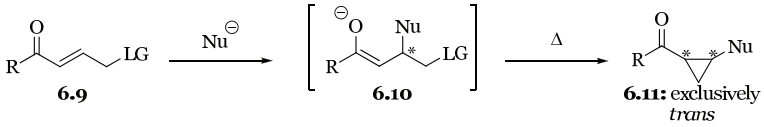
Scheme 6.1. *Total synthesis of phaseolinic acid* ***6.8****.*



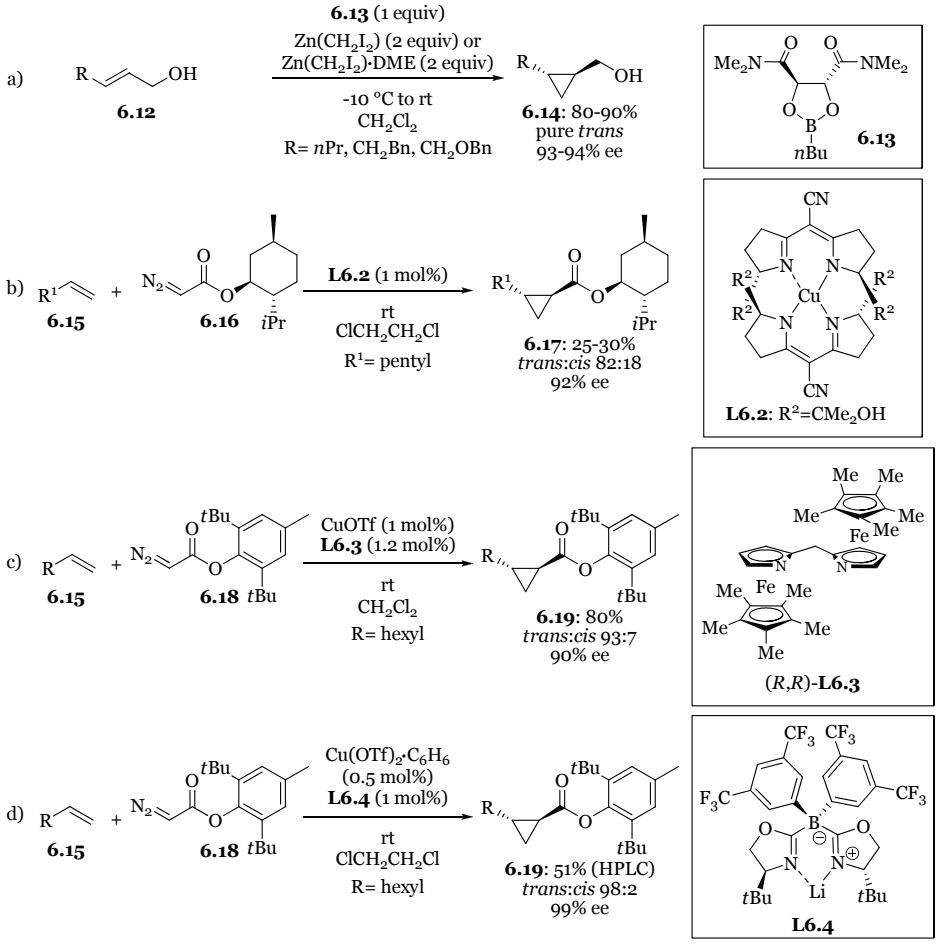
6.2 Synthesis of cyclopropanes via tandem ACA-intramolecular enolate trapping

The enantioselective Simmons-Smith cyclopropanation with a stoichiometric amount of a chiral dioxaborolane described by Charette and co-workers[5] (Scheme 6.2a, next page) is currently the benchmark reaction for the synthesis of *trans* 1-alkyl 2-substituted cyclopropanes. Only few catalytic[6] asymmetric methods[7,8] can compete with this method[5] in view of efficiency and yield (Scheme 6.2b, 6.2c and 6.2d, next page). This is in sharp contrast to the well-known catalytic asymmetric synthesis of *trans* 1-aryl 2-substituted cyclopropanes.[9,10] Although Michael addition-initiated ring-closure reactions (MIRCs, Figure 6.2) are

Figure 6.2. *Michael initiated ring-closure reaction towards trans cyclopropanes.*



Scheme 6.2. *Asymmetric synthesis of trans 1-alkyl 2-substituted cyclopropanes.*



Scheme 6.3. *Asymmetric reactions of 4-halocrotonates with Grignard reagents.*

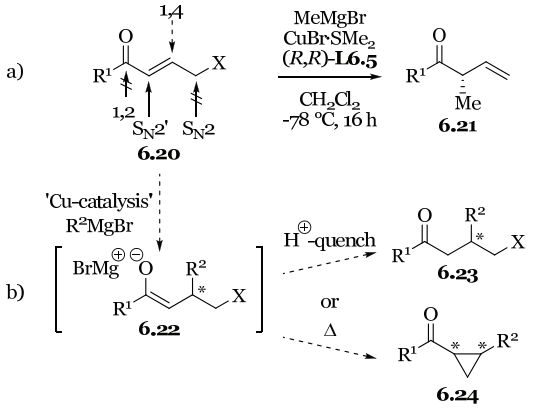
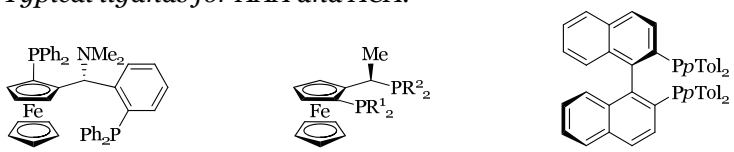


Figure 6.3. *Typical ligands for AAA and ACA.*



(*R*,*R*)-**L6.5**, TaniaPhos (*R*,*S*)-**L6.1**, R¹=Ph, R²=Cy, JosiPhos (*R*)-**L6.7**, TolBINAP
(*R*,*S*)-**L6.6**, R¹=Cy, R²=Ph, reversed JosiPhos

well-known for the diastereo- and enantioselective preparation of substituted cyclopropanes,[9] to our knowledge the use of organometallic reagents for the catalytic asymmetric[11,12] preparation o*f trans* 1,2-disubstituted cyclopropanes[10a,b,e,k] via MIRC[13] is absent in the literature.[9]

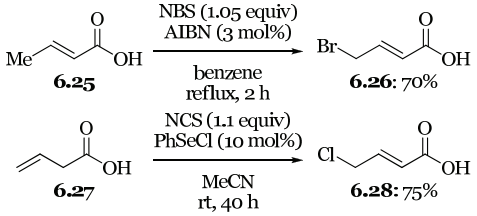
Recently, we explored the asymmetric allylic alkylation[14] (AAA) of 4-halocrotonates using Grignard reagents (Scheme 6.3a).[15] For these substrates, every carbon atom can be targeted by the organometallic reagent. In our recent report, the combined use of Cu-TaniaPhos[16] (**L6.5**, Figure 6.3) and MeMgBr allowed the preparation of α-Me substituted esters in high yield, regio- and enantioselectivity (Scheme 6.3a, R¹=OBn, chapter 5).[15] Here we report the Cu-catalyzed asymmetric 1,4-addition (ACA) of Grignard reagents[14c,d,17] to 4-chlorocrotonates using the readily available Tol-BINAP (**L6.7**) as ligand. This transformation provides a general route to both 4-chloro-3-alkylsubstituted thioesters and ketones (**6.23**, X=Cl) and to *trans* 1,2-disubstituted cyclopropanes (**6.24**, X=Cl) with excellent ee.

6.3 Synthesis of 4-halocrotonates

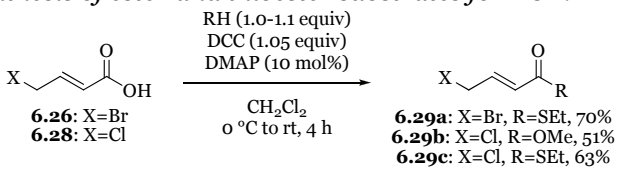
The synthesis of 4-halo α,β-unsaturated esters and thioesters started with the synthesis of 4-halocrotonic acids (Scheme 6.4). 4-Bromocrotonic acid (**6.26**) was obtained via radical bromination in good yield, while 4-chlorocrotonic acid (**6.28**) was obtained in good yield using a Se-catalyzed halogenation[18] with 4-butenoic acid (**6.27**) as substrate.

E-S-ethyl 4-bromobut-2-enethioate (**6.29a**) was obtained via thioesterification of 4-bromocrotonic acid (**6.26**) via carbodiimide mediated coupling in good yield (Scheme 6.5, next page). Esterification[19] of 4-chlorocrotonic acid (**6.28**) gave *E*-methyl 4-chlorobut-2-enoate (**6.29b**) in good yield. Synthesis of *E*-S-ethyl 4-chlorobut-2-enethioate (**6.29c**) was slightly more complicated since thioesterification of 4-chlorocrotonic acid (**6.28**) gave the product **6.29c** with

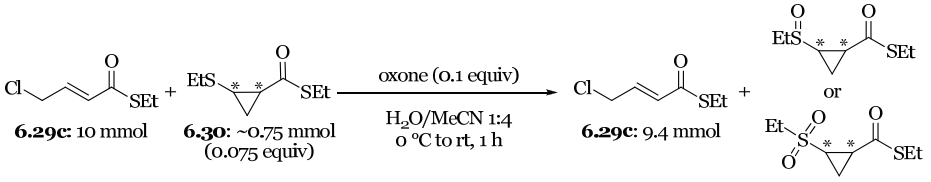
Scheme 6.4. *Synthesis of 4-halocrotonic acids.*



Scheme 6.5. *Synthesis of ester and thioester substrates for ACA.*



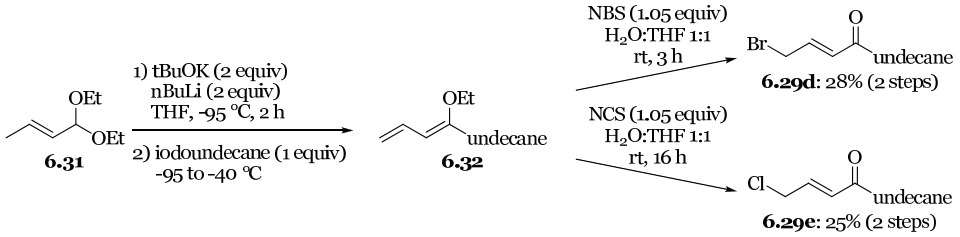
Scheme 6.6. *Purification of E-S-ethyl 4-chlorobut-2-enethioate.*



concomitant *trans* S-ethyl 2-(ethylthio)cyclopropanecarbothioate (**6.30**, Scheme 6.6) which proved inseparable by column chromatography. Subsequent oxidation of the thioether with optimized conditions[ii] allowed separation of the oxidized cyclopropane and allowed recovery of **6.29c** in excellent yield (94%).

Finally, 4-halo α,β-unsaturated aliphatic ketones were prepared[20] from *E*-2-butenal diethyl acetal (**6.31**, Scheme 6.7). Subsequent treatment of **6.31** with the LICKOR superbase (a mixture of nBuLi and *t*BuOK) and iodoundecane gave **6.32**. Finally, treatment of **6.32** with NBS or NCS gave *E*-1-bromopentadec-2-en-4-one (**6.29d**) or *E*-1-chloropentadec-2-en-4-one (**6.29e**), respectively, in low yield over 2 steps.

Scheme 6.7. *Synthesis of 4-halo α,β-unsaturated aliphatic ketones.*



6.4 Asymmetric conjugate addition to 4-halocrotonates

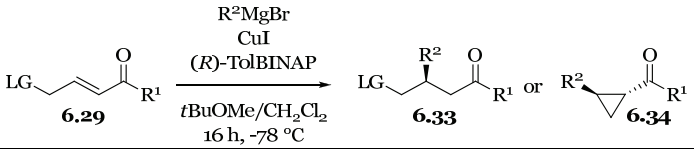
To synthesize *trans* cyclopropanes via tandem ACA-enolate trapping, initially the ACA of Grignard reagents to 4-halocrotonates was studied (Table 6.2). The low yield observed[iii] for the ACA to bromo-substituted substrate **6.29a** (entry 1) prompted us to investigate chloro-substituted substrate **6.29c** for this reaction (entry 2). Addition of hexylmagnesium bromide to **6.29c** using Cu-TolBINAP (**L6.7**) at −78 °C gave, after quenching at this temperature, **6.33c** in good yield (83%) and excellent ee (94%). The addition of phenethylmagnesium bromide to **6.29c** gave

[ii] The use of MeOH as solvent for this reaction led to additional formation of **6.32**.

[iii] The low yield of **6.34a** is mainly due to incomplete conversion of **6.29a** and the competitive formation of ethyl thiocrotonate via halogen-magnesium exchange and subsequent protonation upon work-up.

6.29g in good yield (entry 3, 89%) and good ee (84%). For 4-halo α,β-unsaturated aliphatic ketones and esters similar results were obtained. The reaction of the bromo substituted substrate **6.29d** or **6.29f** with Grignard reagents gave low yield of, respectively, cyclopropanes **6.34d** and **6.34f** (entry 4 and 5). In contrast, the reaction of the 4-chloro substituted α,β-unsaturated ketone **6.29e** gave **6.33e** in good yield (entry 6, 84%) and excellent ee (96%). The Cu-catalyzed reaction of **6.29b** with phenethylmagnesium bromide at −40 °C gave cyclopropane **6.34b**[iv] as main product, along with traces of **6.33b**, in a reasonable combined yield (65%, entry 7) and excellent ee (>95%). Already at −40 °C, the enolate formed from **6.29b** gave slow ring-closure to yield the corresponding cyclopropane, **6.34b**.

Table 6.2. *Substrate screening for ACA to 4-halocrotonates.*[a]



entry	substrate	LG	R¹	R²	product	yield	ee[b]
1	**6.29a**	Br	SEt	hexyl	**6.34a**	<20%[c]	-
2	**6.29c**	Cl	SEt	hexyl	**6.33c**	83%	94%
3	**6.29c**	Cl	SEt	$BnCH_2$	**6.33g**	89%	84%
4	**6.29d**	Br	undecanyl	hexyl	**6.34d**	32%[d]	n.d.
5[e]	**6.29f**	Br	OMe	$BnCH_2$	**6.34f**	<20%[c]	-
6	**6.29e**	Cl	undecanyl	$BnCH_2$[f]	**6.33e**	84%	96%
7[e]	**6.29b**	Cl	OMe	$BnCH_2$	**6.34b**[g]	65%[h]	>95%

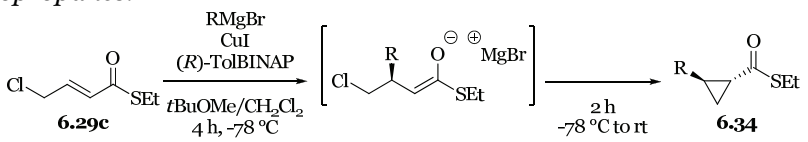
[a] Conditions: **6.29** (0.5 mmol) in CH_2Cl_2 (1 mL) was added over 2 h to a solution of CuI (1 mol%), (*R*)-TolBINAP (**L6.7**, 1.5 mol%) and Grignard reagent (1.2 equiv) in *t*BuOMe (4 mL). [b] Ee was determined by chiral GC or HPLC. [c] Based on GC-MS. [d] 20% of **6.29d** and 18% of the debrominated *E*-pentadec-2-en-4-one were obtained. [e] Reaction was performed at −40 °C, 4 h reaction time. [f] This Grignard reagent was used since no separation was found for the product from the addition of hexylMgBr. [g] In addition traces (<10%) of **6.33b** were obtained. [h] Combined yield of **6.33b** and **6.34b**.

6.5 Grignard reagent and substrate scope for the synthesis of *trans* 1,2-disubstituted cyclopropanes

The formation of cyclopropanes via tandem ACA-enolate trapping was subsequently investigated. The reaction of hexylmagnesium bromide and **6.29c** afforded, after completion of the ACA and warming to rt, cyclopropane **6.34c** in good yield (Table 6.3, next page, entry 1). No detectable racemization was observed since both **6.33c** and **6.34c** were obtained with 94% ee. Precise control of the amount of Grignard reagent is essential to obtain good yield of the cyclopropane. When less than 1.2 equiv of hexylmagnesium bromide was employed, a small but significant amount of acyclic product **6.33b** was obtained.[v] When more than 1.2 equiv of the Grignard reagent was used, in part the cyclopropane product was obtained with additional double 1,2-addition of the Grignard reagent to the thioester moiety.

[iv] To obtain **6.33b** the use of the Cu-JosiPhos (**L6.1**) system at −78 °C might be explored.
[v] This product proved to be inseparable from **6.34c** by column chromatography.

Table 6.3. *Alkyl Grignard reagent scope for tandem ACA-enolate trapping towards trans cyclopropanes.*[a]



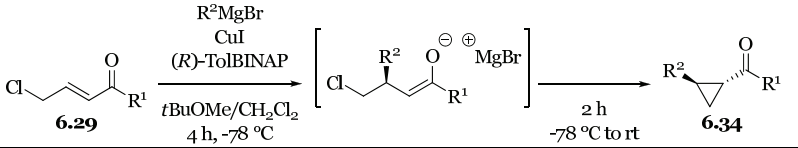
entry	R	product	yield	ee[b]
1	hexyl	**6.34c**	87%	94%
2	Me	**6.34h**	56%	87%
3	Et	**6.34i**	67%	95%
4	*i*Pr	**6.34j**	89%	70%
5	*i*Bu	**6.34k**	91%	84%
6[c]	but-3-enyl	**6.34l**	88%	94%
7	$BnCH_2$	**6.34g**	92%	84%

[a] Conditions: **6.29** (1.0 mmol) in CH_2Cl_2 (2 mL) was added over 2 h to a solution of CuI (1 mol%), (*R*)-TolBINAP (**L6.7**, 1.5 mol%) and Grignard reagent (1.2 equiv) in *t*BuOMe (8 mL). [b] Ee was determined by chiral GC or HPLC. [c] 3.0 mmol scale.

With the procedure for the synthesis of *trans* cyclopropanes developed, the scope[vi] of the alkyl Grignard reagents of this transformation was explored. The use of both MeMgBr and EtMgBr gave the corresponding volatile *trans* cyclopropanes **6.34h** and **6.34i** in slightly lower yield and in good to excellent ee (entry 2 and 3). The Cu-catalyzed transformation of **6.29c** with the sterically encumbered Grignard reagents *i*PrMgBr and *i*BuMgBr gave the corresponding cyclopropanes **6.34j** and **6.34k** in somewhat lower ee but good yield (entry 4 and 5). Finally, two functionalized Grignard reagents gave cyclopropanes **6.34l** and **6.34g** in good yield and ee (entry 6 and 7).

Also ketone substrate **6.29e** gave, upon allowing the reaction mixture to reach rt, the corresponding cyclopropane in good yield and ee (Table 6.4, entry 1). Furthermore, the reaction of **6.29e** with MeMgBr gave cyclopropane **6.34m** in excellent yield and ee (entry 2). Finally, when the reaction mixture of **6.29b** and phenethylmagnesium bromide was allowed to warm to rt, exclusively cyclopropane **6.34b** was obtained in reasonable yield and excellent ee (entry 3).

Table 6.4. *Scope of electron withdrawing group for tandem ACA-enolate trapping towards trans cyclopropanes.*[a]



entry	substrate	R^1	R^2	product	yield	ee[b]
1	**6.29e**	undecanyl	$BnCH_2$	**6.34e**	75%	96%
2	**6.29e**	undecanyl	Me	**6.34m**	87%	98%
3	**6.29b**	OMe	$BnCH_2$	**6.34b**	68%	>95%

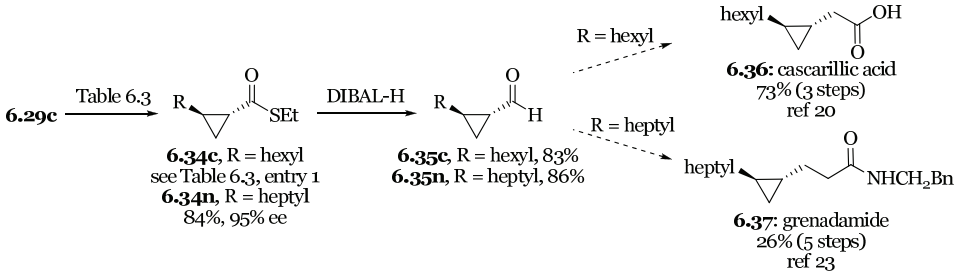
[a] For conditions see Table 6.3. [b] Ee was determined by chiral GC or HPLC.

[vi] Aryl Grignard reagents have not been studied for this transformation.

6.6 Formal syntheses of cascarillic acid and grenadamide

To illustrate the versatility of the developed method, cyclopropane **6.34c** was selectively reduced to the aldehyde **6.35c** in good yield (Scheme 6.8). **6.35c** is an intermediate in a reported synthesis[21] of cascarillic acid (**6.36**).[22,23] Cascarillic acid is extracted from bark of the shrub *Croton eluteria* and is part of cascarilla essential oil. This oil has been used for the treatment of colds, influenza and bronchitis. Furthermore, the reaction of **6.29c** with heptylmagnesium bromide gave cyclopropane **6.34n** in good yield and ee (Scheme 6.8). Reduction of **6.34n** to the aldehyde **6.35n** gave an intermediate for the synthesis[24] of another natural product, grenadamide (**6.36**).[25, 26] Grenadamide can bind to cannabinoid receptors (K_i=4.7 μM) and has modest toxicity for marine organism (brine shrimp toxicity LD_{50}= 5 μg/mL).[26]

Scheme 6.8. *Formal syntheses of cascarillic acid and grenadamide.*[a]

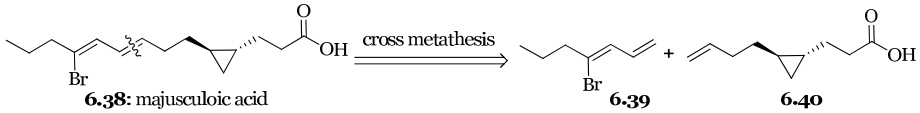


[a] Conditions: **6.34**: See Table 6.3; **6.35**: **6.34**, DIBAL-H (1.0 M solution in CH_2Cl_2, 1.2 equiv) in CH_2Cl_2 (0.4 M in **6.34**), −78 °C, 3 h.

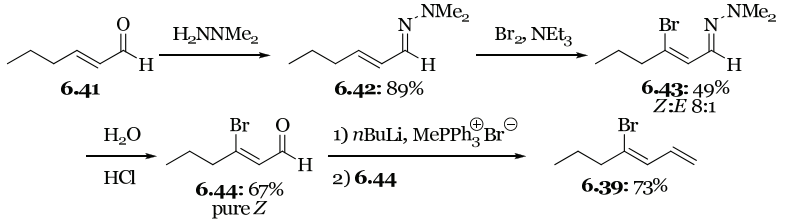
6.7 A synthetic route to majusculoic acid

Majusculoic acid (**6.38**) has recently been isolated from a marine cyanobacterial mat assemblage and exhibits antifungal activity against *Candida albicans* ATCC 14503.[27] No synthesis route for this natural product is known. Interestingly, the structure of **6.38** incorporates a *trans* 1-alkyl-2 substituted cyclopropane. In a retrosynthetic analysis **6.38** is divided in a side-chain part **6.39** and the *trans* cyclopropane part **6.40** which will be connected via cross metathesis (Scheme 6.9).

Scheme 6.9. *Retrosynthetic analysis of majusculoic acid.*



Scheme 6.10. *Synthesis of the side-chain of majusculoic acid.*[a]

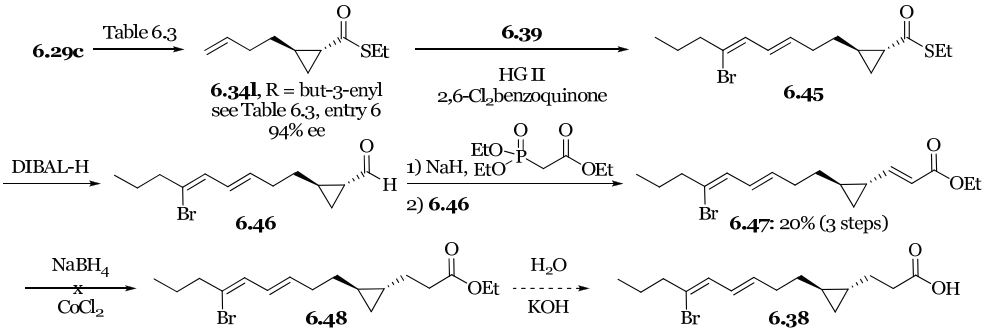


[a] Conditions: **6.42**: **6.41**, H_2NNMe_2 (1.05 equiv), CH_2Cl_2 (0.1 M in **6.41**), rt, 40 h; **6.43**: **6.42**, Br_2 (1.05 equiv), NEt_3 (1.05 equiv), CH_2Cl_2 (0.25 M in **6.42**), −20 to −10 °C, 2 h; **6.44**: **6.43**, aq HCl solution (0.1 M in **6.43**), pentane (0.1 M in **6.43**), rt, 16 h; **6.40**: 1) $MePPh_3$-Br (1.5 equiv), *n*BuLi (1.6 M in hexanes), THF (0.1 M in $MePPh_3$-Br), 0 °C, 1 h; 2) **6.44**, 0 °C, 0.5 h.

The synthesis of the side-chain **6.39** (Scheme 6.10) started with the formation of the hydrazone **6.42** from *E*-2-hexenal (**6.41**) in good yield (89%).[28] Subsequent bromination[29] gave the β-brominated product **6.43** in reasonable yield (49%) as a mixture of *Z*- and *E*-product (8:1). Hydrolysis[30] of the hydrazone gave aldehyde **6.44** in good yield (67%) and at this stage the *Z*- and *E*-product could be separated. Finally, Wittig reaction[31] of **6.44** gave diene **6.39** in good yield (73%). It proved necessary to synthesize **6.39** immediately before the cross metathesis since it degraded upon storage overnight at −20 °C.

Synthesis of the cyclopropane part started with the formation of **6.34l** (Scheme 6.11) described earlier in this chapter (Table 6.3). Subsequent cross metathesis,[32] using dichlorobenzoquinone[33] as an additive to quench undesired radicals and prevent the formation of a RuH species, gave product **6.45** with 80% conversion and around 50% yield. The low yield can be explained by formation of a significant amount of the homocoupling product of **6.34l**. Reduction of the thioester and subsequent HWE reaction[34] of **6.46** gave **6.47** in low yield (20% over 3 steps). An initial attempt to perform conjugate reduction of **6.47** using a Co-catalyzed $NaBH_4$ reduction[35,36] led to trace amounts of product **6.48**. Upon storage for 4 days at −20 °C, the remainder of **6.47** had degraded; the diene could not be observed anymore by ^{1}H-NMR.

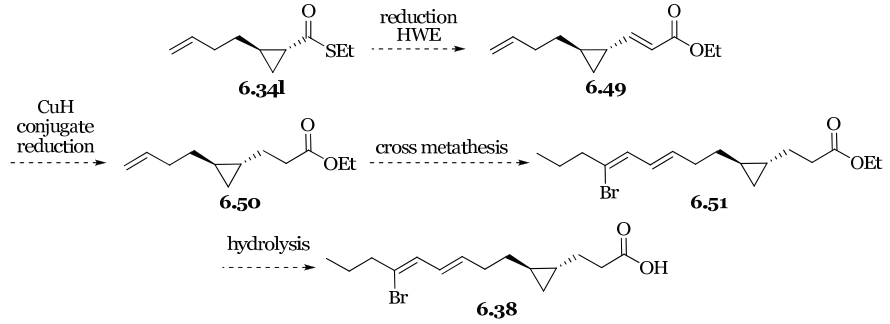
Scheme 6.11. *Attempted synthesis of majusculoic acid.*[a]



[a] Conditions: **6.34l**: See Table 6.3; **6.45**: **6.34l**, **6.40** (2.7 equiv), HGII (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH_2Cl_2 (1.1 M in **6.34l**), 40 °C, 16 h; **6.46**: see Scheme 6.8; **6.47**: 1) $(EtO)_2POCH_2CO_2Et$ (1.75 equiv), NaH (1.75 equiv), THF (1.75 M in $(EtO)_2POCH_2CO_2Et$), −20 °C, 30 min, 2) **6.46**, THF (10 M in **6.46**), −20 °C, 20 min, rt, 30 min; **6.48**: 1) **6.47**, $CoCl_2$ (20 mol%), MeOH (0.25 M in **6.47**), rt, 30 min, 2) $NaBH_4$ (2 equiv), DMF (1 M in $NaBH_4$), rt, 30 min.

The lability of the diene leads to a proposal for an improved synthetic route depicted in Scheme 6.12. In this route first the eastern part of the molecule is prepared and only then the cyclopropane part and the side chain are connected. Unfortunately, time pressure did not allow the improved synthesis route to be tested.

Scheme 6.12. *Proposed route for the synthesis of majusculoic acid.*

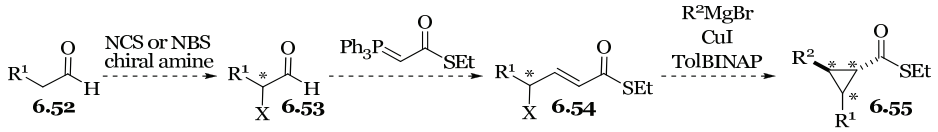


6.8 Towards asymmetric catalytic synthesis of 1,2,3-substituted cyclopropanes

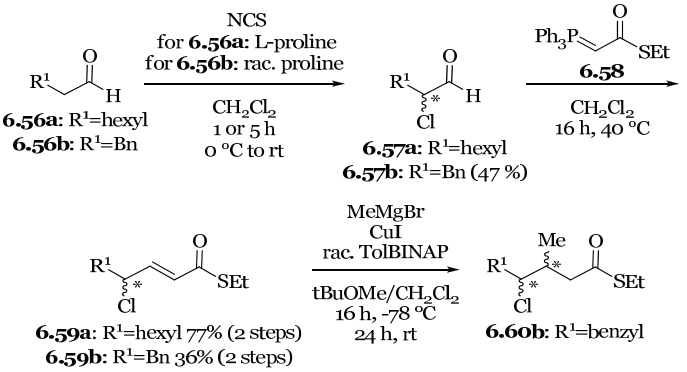
1,2,3-Trisubstituted cyclopropanes are found in numerous biologically active compounds.[10d] Although few synthetic routes[10d,37] exist for the enantio- and diastereoselective construction of the cyclopropane unit, alternative routes are desired. Combining organocatalysis, for either enantioselective α-chlorination[38] or α-bromination[39] of aldehydes, and the Cu-catalyzed ACA-trapping reaction, a straightforward route to 1,2,3-trisubstituted cyclopropanes with control over all stereocenters can be envisioned (Scheme 6.13).

Two substrates for synthesis of 1,2,3-trisubstituted cyclopropanes via ACA-trapping reaction were prepared (Scheme 6.14, next page). Using the protocol described by Jørgensen and co-workers[38] for α-chlorination of aldehydes and subsequent Wittig reaction the warranted hexyl- (**6.59a**) and benzyl-substituted (**6.59b**) substrates were obtained in, respectively, good and reasonable yield over 2 steps. An initial experiment with **6.59b** as substrate gave the 4-chloro substituted ACA product **6.60b** with only traces of the ring-closed product. Further optimization of the conditions for the intramolecular enolate trapping is needed to allow synthesis of 1,2,3-trisubstituted cyclopropanes via this synthetic route.

Scheme 6.13. *Envisioned synthesis route to 1,2,3-trisubstituted cyclopropanes.*



Scheme 6.14. *Synthesis of 4-chloro-4-alkylthiocrotonates.*[a]



[a] Conditions: **6.57**: **6.56**, CH_2Cl_2 (0.5 M in **6.56**), 0 °C to rt, for **6.57a**: NCS (1.3 equiv), L-proline (10 mol%), 1 h, for **6.57b**: NCS (1.5 equiv), rac. proline (50 mol%), 5 h; **6.59**: **6.57**, **6.58** (1.3 equiv), CH_2Cl_2 (0.16 M in **6.57**), 40 °C, 16 h; **6.60**: see Table 6.3.

6.9 Conclusion

In summary, a versatile synthesis of enantiomerically enriched 4-chloro-3-alkylsubstituted thioesters and ketones and *trans* 1-alkyl-2-substituted cyclopropanes is reported. The Grignard reagent and substrate scope comprise aliphatic Grignard reagents and α,β-unsaturated esters, α,β-unsaturated thioesters and α,β-unsaturated aliphatic ketones.

The trans cyclopropane products of this transformation have been elaborated to intermediates for the synthesis of cascarillic acid and grenadamide. Furthermore, one of the *trans* cyclopropane products is an excellent precursor for the asymmetric total synthesis of majusculoic acid. Initial experiments to complete the total synthesis of the latter natural product have been unsuccessful so far due to instability of the intermediates. However, an improved synthetic route has been proposed.

Finally, the described methodology for the synthesis of cyclopropanes might be extended to the enantioselective synthesis of 1,2,3-trisubstituted cyclopropanes and a synthesis route for the required substrates has been reported.

6.10 Perspective and outlook

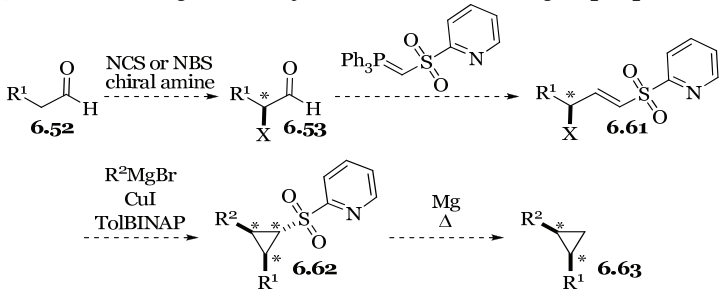
Compared to the other methods for the construction of *trans* 1-alkyl 2-substituted cyclopropanes,[5,7] the methodology described in this chapter is an improvement. Where the previously known asymmetric catalytic methods employ complicated chiral ligands, in the tandem ACA-enolate trapping a (simple) commercially available ligand is employed, improving the accessibility of this methodology. Furthermore, synthesis of *trans* 1-alkyl 2-substituted cyclopropanes via the Simmons-Smith reaction[5] has to be performed at small scale (<1.0 mmol scale advised) due to an observed violent and highly exothermic reaction at 8.0 mmol scale. In contrast the tandem ACA-enolate trapping has shown to be

scalable to 3.0 mmol scale and results for the ACA[40] have shown that this reaction is scalable to larger amounts.

Further research in the ACA-enolate trapping should be directed at identifying the full scope of this methodology for the synthesis of *trans* 1,2-substituted cyclopropanes, which presumably comprises all the employed Grignard reagents for addition to esters,[17c,e,g] thioesters[17d,f] and aliphatic ketones[17b] and possibly aryl Grignard reagents.[41] Furthermore, expanding this methodology towards the enantioselective synthesis of 1,2,3-trisubstituted cyclopropanes (see paragraph 6.8) and preparation of larger ring systems, i. e. cyclopentanes and cyclohexanes, using the procedure described in this chapter can be explored. Another topic for research would be elaboration of the enantioenriched 4-chloro 3-alkyl substituted ACA products to prepare 5-membered heterocycles.

Although *trans* 1,2-disubstituted cyclopropanes are encountered in nature, especially *cis* 1,2-disubstituted are prominently present in nature. The synthesis of *cis* 1,2-disubstituted cyclopropanes might be envisioned via a tandem ACA-enolate trapping reaction to 4-halo α,β-unsaturated sulphones[42] (Scheme 6.14), combining organocatalytic asymmetric α-halogenation of aldehydes,[38,39] Cu-catalyzed ACA-enolate trapping and removal of the sulphone[43] in the final stage. Since the remaining stereogenic centres in the cyclopropane are controlled by asymmetric catalysis this sequence can be tuned to give either the *cis*- or the *trans*-cyclopropane.

Scheme 6.14. *Envisioned synthesis of cis 1,2-substituted cyclopropanes.*



Finally, although the chemistry of zinc and lithium enolates is well-known, the chemistry of magnesium enolates is relatively unexplored and further research to understand the reactivity of magnesium enolates is required to fully exploit the possibilities of tandem ACA-enolate trapping reactions.

6.11 Acknowledgement

Dr. B. Maciá is acknowledged for the preparation of two racemic cyclopropanes. Dr. B. Maciá and Dr. A. Rudolph are acknowledged for their part in the attempted synthesis of majusculoic acid.

6.12 Experimental section

General procedures: All reactions under a N_2 atmosphere were conducted using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under a N_2 atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under N_2 prior to use. Et_2O was distilled from Na using benzophenone as indicator under a N_2 atmosphere prior to use. *t*BuOMe was distilled from CaH_2 under a N_2 atmosphere prior to use. CuI was purchased from Sigma-Aldrich. (*R*)-TolBINAP and (*S*)-TolBINAP were purchased from Sigma-Aldrich. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, *i*BuMgBr and hexylMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et_2O following standard procedures. Grignard reagents were titrated using *s*BuOH and catalytic amounts of 1,10-phenanthroline before use.
3-Butenoic acid, PhSeCl, crotonic acid, DIC, DCC, EtSH, OXONE®, *t*BuOK, *E*-2-butenal diethyl acetal, DIBAL-H, bromine, methyltriphenylphosphonium bromide, 2,6-dichlorobenzoquinone, HG-II catalyst, NaH (60% dispersion in mineral oil), triethyl phosphonoacetate, $NaBH_4$, octanal, *L*-proline and racemic proline were purchased from Sigma-Aldrich. MeCN, DMAP, *n*BuLi, iodoundecane, *E*-2-hexenal, 1,1-dimethylhydrazine, $CoCl_2$ and hydrocinnamylaldehyde were purchased from ACROS. MeOH was purchased from Lab-Scan. Azobis(isobutyronitrile) was purchased from Janssen Chimica. Triethylamine was purchased from Merck.
E-methyl 4-bromobut-2-enoate was purchased from Sigma-Aldrich and was purified by flash column chromatography (eluent 1:99 Et_2O:pentane) prior to use. NCS was purchased from Sigma-Aldrich and was purified by recrystallization from AcOH prior to use. NBS was purchased from Sigma-Aldrich and was purified by recrystallization from H_2O prior to use. S-ethyl 2-(triphenylphosphoranylidene)ethanethioate was prepared as described in ref 44.
Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F_{254} silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). *Ee* and regioselectivities were determined by chiral GC (HP6890, Chiralsil DEX-CB 25 m x 0.25 mm x 0.25 μm; HP6890, Chiraldex G-TA 30 m x 0.25 mm x 0.25 μm) using flame ionization detection or HPLC analysis (chiralcel OB-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm; chiralcel OJ-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm) (in comparison to authentic samples of racemates of the products). Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 for hydrogen atoms, δ = 77.16 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a FTMS Orbitrap Fischer Scientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA).

Synthesis of substrates:
Chlorination of 3-butenoic acid:[18]
The procedure described in ref 18 was followed. 40 mmol scale, omitting mol sieves, 75% yield, instead of column chromatography the product was recrystallized from Et_2O:pentane 1:4.
E-4-chlorobut-2-enoic acid (4-chlorocrotonic acid) (**6.28**) data in accordance with data described in ref 18.

Formation of the methyl ester from 4-chlorocrotonic acid:[19]
In a dried roundbottom two necked flask equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv) and DMAP (0.1 equiv) were dissolved in anhydrous CH_2Cl_2 (5.0 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and subsequently MeOH (1.2 equiv) and DIC (1.05 equiv) were added. After stirring for 4 h (0 °C to rt) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract were dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:199 to 2:98 Et_2O:pentane) yielded the product as a colorless oil.

E-methyl 4-chlorobut-2-enoate (**6.29b**); data in accordance with data described in ref 45.
[8.5 mmol scale, 51% yield (presumably due to volatility), colorless oil]

General procedure for the formation of thioesters from α,β-unsaturated carboxylic acids:
In a dried roundbottom two necked flask equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv) and DMAP (0.1 equiv) were dissolved in anhydrous CH_2Cl_2 (1.5 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and subsequently EtSH (1 equiv) and DCC (1.05 equiv) in CH_2Cl_2 (0.5 mL/mmol substrate)[vii] were added. After stirring for 4 h (0 °C to rt) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract were dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 4:96 Et_2O:pentane) yielded the product as a colorless oil with a slight impurity (5-10% of presumably *trans* S-ethyl 2-(ethylthio)cyclopropanecarbothioate (**6.30**)).

Further purification of *E*-S-ethyl 4-chlorobut-2-enethioate (**6.29c**):[viii]
In a roundbottom flask equipped with septum and stirring bar, the substrate (~90% product and ~10% side product) was dissolved in a mixture of H_2O and MeCN (1:4 3.0 mL/mmol substrate). The mixture was cooled to 0 °C and OXONE® (49% active O_2, 0.1 equiv) was added. After vigorous stirring for 20 min the reaction mixture was warmed to rt and vigorously stirred for another 40 min. Subsequently the reaction was quenched at 0 °C with brine (10 mL/mmol substrate) and the reaction mixture was extracted with Et_2O (3x 10 mL/mmol substrate), the combined organic extracts were dried and concentrated to a colorless oil. Flash column chromatography (gradient 1:199 to 2:98 Et_2O:pentane) yielded the product as a colorless oil.

E-S-ethyl 4-chlorobut-2-enethioate (**6.29c**):
[45 mmol scale, 63% yield, colorless oil]
[Further purification of by ^{1}H NMR estimated 10 mmol scale + 0.75 mmol side product, 94% yield (9.4 mmol product), colorless oil]
^{1}H NMR δ 6.81 (dt, *J*= 15.1 Hz, 6.0 Hz, 1H), 6.29 (dd, *J*= 15.2 Hz, 1.4 Hz, 1H), 4.11 (d, *J*= 6.0 Hz, 2H), 2.90 (q, *J*= 7.4 Hz, 2H), 1.22 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 189.36 (C), 137.31 (CH), 130.52 (CH), 42.65 (CH_2), 23.48 (CH_2), 14.73 (CH_3); MS *m/z* 166 ($M^+[Cl^{37}]$, 2), 164 ($M^+[Cl^{35}]$, 6), 105 ($M^+[Cl^{37}]$-SEt, 33), 103 ($M^+[Cl^{35}]$-SEt, 100), 75 ($M^+[Cl^{35}]$-COSEt, 20); HRMS calcd. for $C_6H_{10}ClOS$ 165.0135, found 165.0132.

Bromination of crotonic acid was performed according to ref 15.
E-4-bromobut-2-enoic acid (**6.26**, 4-bromocrotonic acid) data in accordance with data described in ref 15.
[230 mmol scale, 70% yield, white solid, mp: 74.7-75.3 °C].

Thioesterification of 4-bromocrotonic acid was performed according to the general procedure for the formation of thioesters from α,β-unsaturated carboxylic acids using DCC.

[vii] Alternatively DIC (1.05 equiv) was used with comparable results.
[viii] The non pure *E*-S-ethyl 4-chlorobut-2-enethioate (**6.29c**) has been used for the intramolecular 1,4-addition without any influence on the *ee*.

E-S-ethyl 4-bromobut-2-enethioate (**6.29a**); data in accordance with data described in ref 46.
Purified by flash chromatography (1:99 Et_2O:pentane).
[21 mmol scale, 70% yield, colorless oil]

General procedure for the formation of 1-chloro 2-en-4-ones:[20]
1. Synthesis of *E*-4-ethoxypentadeca-1,3-diene (**6.32**):
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere *t*BuOK (2.0 equiv) was dissolved in anhydrous THF (1.5 mL/mmol substrate). The mixture was cooled to −78 °C and *E*-2-butenal diethyl acetal (1.0 equiv) was added dropwise. The reaction mixture was cooled to −95 °C and *n*BuLi (1.6 m in hexanes, 2.0 equiv) was added dropwise. After stirring for 2 h at rt the reaction mixture was treated with the iodoalkane (1 equiv) and allowed to warm up to −40 °C slowly. Then the reaction was quenched with a mixture of water and THF (1:1, 2.0 mL/mmol substrate). The aqueous phase was extracted with Et_2O (3x 3.0 mL/mmol substrate) and then the organic extracts were washed with brine (1x 3.0 mL/mmol substrate), dried and concentrated to a yellow oil. The product was used directly in the next step.

2. Electrophilic trapping of ethoxypentadeca-1,3-diene:
In a dried roundbottom flask equipped with septum and stirring bar the substrate (1.0 equiv) was dissolved in a mixture of water and THF (1: 1 4.0 mL/mmol substrate). The reaction mixture was cooled to 0 °C and NCS (1.05 equiv) was added. After stirring for 16 h the reaction mixture was treated with an aq 5% $NaHCO_3$ solution (1x 4.0 mL/mmol substrate) and extracted with Et_2O (3x 4.0 mL/mmol substrate). The organic extract were washed with brine (1x 4.0 mL/mmol substrate), dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 2:98 Et_2O:pentane) yielded the product.

E-1-chloropentadec-2-en-4-one (**6.29e**):
[Iodoundecane was used, 33 mmol scale, 25% yield (2 steps), off-white solid, mp: 39.6 °C].
^{1}H NMR δ 6.80-6.70 (m, 1H), 6.27 (dt, *J*= 15.6 Hz, 1.5 Hz, 1H), 4.15-4.08 (m, 2H), 2.49 (t, *J*= 7.4 Hz, 2H), 1.60-1.48 (m, 2H), 1.29-1.09 (m, 16H), 0.81 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 199.63 (C), 139.12 (CH), 131.49 (CH), 42.90 (CH_2), 40.88 (CH_2), 31.90 (CH_2), 29.60 (2x CH_2), 29.47 (CH_2), 29.41 (CH_2), 29.33 (CH_2), 29.20 (CH_2), 23.90 (CH_2), 22.67 (CH_2), 14.09 (CH_3); Anal. Calc. for $C_{15}H_{27}ClO$: C, 69.61; H, 10.51; Found: C, 69.68, H, 10.65; MS *m/z* 223 (M^+-Cl, 1), 222 (M^+-Cl, 6), 95 (C_6H_7O, 49), 82 (C_5H_6O, 38), 81 (C_5H_5O, 100); HRMS calcd. for $C_{15}H_{28}ClO$ 259.1823, found 259.1817.

E-1-bromopentadec-2-en-4-one (**6.29d**):
[The general procedure for the formation of 1-chloro 2-en-4-ones was followed using iodoundecane, NCS was replaced by NBS, 3 h reaction time was used for the trapping, 5 mmol scale, 28 % yield (2 steps), slightly brown solid, mp: 40.9-41.2 °C]
^{1}H NMR δ 6.82 (dt, *J*= 15.6 Hz, 7.3 Hz, 1H), 6.23 (dt, *J*= 15.6 Hz, 1.2 Hz, 1H), 4.00 (dd, *J*= 7.3 Hz, 1.2 Hz, 2H), 2.53 (t, *J*= 7.4 Hz, 2H), 1.64-1.52 (m, 2H), 1.33-1.12 (m, 16H), 0.85 (t, *J*= 6.9 Hz, 3H); ^{13}C NMR δ 199.93 (C), 139.30 (CH), 132.15 (CH), 40.84 (CH_2), 31.98 (CH_2), 29.83 (CH_2), 29.68 (2x CH_2), 29.55 (CH_2), 29.49 (CH_2), 29.41 (CH_2), 29.29 (CH_2), 24.02 (CH_2), 22.77 (CH_2), 14.20 (CH_3); Anal. Calc. for $C_{15}H_{27}BrO$: C, 59.40; H, 8.97; Found: C, 59.40, H, 8.90; MS *m/z* 261 (M^+[^{81}Br]-Pr, 1), 259 (M^+[^{79}Br]-Pr, 1), 209 (M^+-CH_2Br, 34), 120 (C_3H_3[^{81}Br], 34), 118 (C_3H_3[^{79}Br], 100), 103 (C_2[^{79}Br], 66), 83 (C_5H_7O, 39); HRMS calcd. for $C_{15}H_{27}{}^{79}BrONa$ 325.1138, found 325.1129, calcd. for $C_{15}H_{27}{}^{81}BrONa$ 327.1117, found 327.1108.

General procedure for the Cu-catalyzed 1,4-addition of Grignard reagent to 4-chlorocrotonates leading to 4-chloro 3-substituted butenoates:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the premade[ix] catalyst of CuI (1 mol%) and (*R*)-Tol-BINAP (1.5 mol%) was cooled to −78 °C and the Grignard reagent (1-3 M solution in Et_2O, 1.10 or 1.15 equiv[x]) was added. After stirring for 10 min, a solution of the substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 2.0 mL/mmol substrate) was added over 2 h with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at −78 °C.
Subsequently the reaction mixture was quenched at −78 °C with EtOH (0,4 mL/mmol substrate), followed by a 1 M aq NH_4Cl-solution (2 mL/mmol substrate) and was allowed to warm to rt. Then a 1 M aq NH_4Cl-solution (additional 10 mL/mmol substrate) and Et_2O (10 mL/mmol substrate) were added and the layers were separated. After extraction with Et_2O (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:99 Et_2O:pentane) yielded the product as a colorless oil.

(*S*)-S-ethyl 3-(chloromethyl)nonanethioate (**6.33c**):
[0.5 mmol scale, 83% yield, 94% ee, colorless oil]
$[\alpha]_D^{20}$ = +4.5 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 3.63-3.50 (m, 2H), 2.86 (q, *J*= 7.5 Hz, 2H), 2.63 (ddd, *J*= 21.6 Hz, 15.5 Hz, 6.7 Hz, 2H), 2.35-2.22 (m, 1H), 1.50-1.09 (m, 13H), 0.86 (t, *J*= 6.7 Hz, 3H); ^{13}C NMR δ 198.51 (C), 48.11 (CH_2), 46.16 (CH_2), 37.56 (CH), 31.78 (CH_2), 31.48 (CH_2), 29.31 (CH_2), 26.60 (CH_2), 23.50 (CH_2), 22.68 (CH_2), 14.81 (CH_3), 14.16 (CH_3); MS *m/z* 223 (M^+[^{37}Cl]-Et , 1), 221 (M^+[^{35}Cl]-Et, 4), 191 (M^+[^{37}Cl]-Et , 33), 189 (M^+[^{35}Cl]-Et ,100), 69 (C_4H_5O, 38); HRMS calcd. for $C_{12}H_{24}ClOS$ 251.1231, found 251.1227; *Ee* was determined by chiral GC analysis of methyl 3-(chloromethyl)nonanoate,[xi] column: Chiraldex-G-TA, 90 °C for 15 min, 90 °C to 170 °C in 40 min, retention times (min): 34.4 (*R*-enantiomer), 34.7 (*S*-enantiomer).

(*S*)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate (**6.33g**) was prepared via the general procedure for the Cu-catalyzed 1,4-addition of Grignard reagent to 4-chlorocrotonates leading to 4-chloro 3-substituted butenoates:
[0.25 mmol scale, 89% yield, 84% ee, colorless oil]
$[\alpha]_D^{20}$: −3.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 7.34-7.26 (m, 2H), 7.24-7.16 (m, 3H), 3.66 (d, *J*= 4.5 Hz, 2H), 2.91 (q, *J*= 7.4 Hz, 2H), 2.80 (dd, *J*= 15.5 Hz, 7.3 Hz, 1H), 2.74-2.58 (m, 3H), 2.45-2.34 (m, 1H), 1.89-1.66 (m, 2H), 1.27 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 198.32 (C), 141.48 (C), 128.58 (CH), 128.41 (CH), 126.15 (CH), 47.91 (CH_2), 45.98 (CH_2), 37.09 (CH), 33.22 (CH_2), 32.95 (CH_2), 23.58 (CH_2), 14.83 (CH_3); MS *m/z* 211 (M^+[^{37}Cl]-SEt, 16), 210 (M^+[^{37}Cl]-HSEt, 39), 209 (M^+[^{35}Cl]-SEt , 48), 208 (M^+[^{35}Cl]-HSEt, 39), 129 (C_6H_9OS , 80), 91 (C_7H_7 ,100); HRMS calcd. for $C_{14}H_{20}ClOS$ 271.0918, found 271.0896; *Ee* was determined by chiral HPLC analysis for methyl 3-(chloromethyl)-5-phenylpentanoate,[xi] column: chiralcel OB-H, (99:1 heptane:*i*PrOH); retention times (min): 26.0 (*S*-enantiomer), 32.7 (*R*-enantiomer).

[ix] CuI (1 mol%) and (*R*)-TolBINAP (1.5 mol%) were dissolved in anhydrous *t*BuOMe (8 mL/mmol substrate) and stirred for 1 h to give a clear yellow solution, the solutions were stored under a N_2 atmosphere until use; usually stock solutions for 3-5 mmol substrate were prepared and these solutions have been used after 7 days without change in reactivity

[x] The amount of Grignard reagent is extremely important, just enough is needed to prevent protonolysis of the enolate (by traces of water in the reaction mixture and presumably another mechanism). An excess will lead to subsequent double alkylation via 1,2-addition of the products.

[xi] Transesterification was performed via the following procedure; The substrate (~10 mg) was dissolved in MeOH (0.5 mL) and stirred for 3 h in the presence of K_2CO_3 (excess), then an aq NH_4Cl-solution (1 M, 0.5 mL) was added and the layers were separated. After extraction with Et_2O (2x 0.5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Filtration over a short SiO_2-column (eluent Et_2O) and evaporation of the solvent yielded the product as a colorless oil.

(*S*)-3-(chloromethyl)-1-phenylhexadecan-5-one (**6.33e**):
[0.5 mmol scale, 84% yield, 96% ee, colorless oil (which becomes a white solid after storage at −20 °C, with melting point around 20 °C)]
$[\alpha]_D^{20}$ = −5.4 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 7.34-7.25 (m, 2H), 7.23-7.16 (m, 3H), 3.66 (dd, *J*= 3.9 Hz, 1.4 Hz, 2H), 2.75-2.54 (m, 3H), 2.49-2.36 (m, 4H), 1.85-1.52 (m, 4H), 1.37-1.22 (m, 16H), 0.96-0.87 (m, 3H); ^{13}C NMR δ 209.88 (C), 141.58 (C), 128.45 (CH), 128.29 (CH), 125.98 (CH), 48.35 (CH_2), 44.46 (CH_2), 43.47 (CH_2), 34.90 (CH), 33.41 (CH_2), 33.04 (CH_2), 31.93 (CH_2), 29.63 (2x CH_2), 29.49 (CH_2), 29.42 (CH_2), 29.36 (CH_2), 29.22 (CH_2), 23.85 (CH_2), 22.71 (CH_2), 14.15 (CH_3); MS *m/z* 328 (M^+-H-Cl, 14), 223 ($C_{15}H_{27}O$, 100), 207 ($C_{14}H_{25}O$, 45), 129 (29), 91 (C_7H_7, 23); HRMS (APCI positive mode) calcd. for $C_{23}H_{38}ClO$ 365.2606, found 365.2601; The *ee* corresponds to the *ee* for 1-((1*R*,2*R*)-2-phenethylcyclopropyl)dodecan-1-one (vide infra).

General procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to *trans* 2-substituted cyclopropanecarbothioates:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the premade catalyst (CuI (1 mol%); (*R*)-TolBINAP (1.5 mol%); anhydrous *t*BuOMe (8 mL/mmol substrate)) was cooled to −78 °C and the Grignard reagent (1-3 M solution in Et_2O, 1.10 or 1.15 equiv) was added. After stirring for 10 min, a solution of the substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 2.0 mL/mmol substrate) was added in 2 h to 2 h 15 min with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at −78 °C. Subsequently the reaction mixture was allowed to warm up to rt and stirred for an additional 2 h. Then the reaction mixture was treated with EtOH (0,4 mL/mmol substrate), followed by a 1 M aq NH_4Cl-solution (2 mL/mmol substrate). A 1 M aq NH_4Cl-solution (additional 10 mL/mmol substrate) and Et_2O (10 mL/mmol substrate) were added and the layers were separated. After extraction with Et_2O (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:99 Et_2O:pentane) yielded the product as a colorless oil.

The *trans* configuration of the cyclopropanes was established by comparison of the spectra for *cis* and *trans* 2-heptylcyclopropanecarbaldehyde and the spectrum of *trans* 2-heptylcyclopropanecarbaldehyde (**6.35n**) obtained using our route. Furthermore, ^{1}H NOESY experiments (vide supra) performed with (1*R*,2*R*)-S-ethyl 2-methylcyclopropanecarbothioate (**6.34h**) also confirms the *trans* configuration.

(1*R*,2*R*)-S-ethyl 2-hexylcyclopropanecarbothioate (**6.34c**):
[1.0 mmol scale, 87% yield, 94% ee, colorless oil]
$[\alpha]_D^{20}$ =: −107.2 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.85 (dt, *J*= 8.2 Hz, 6.8 Hz, 2H), 1.71 (dt, *J*= 8.1 Hz, 4.2 Hz, 1H), 1.56-1.41 (m, 1H), 1.41-1.06 (m, 14H), 0.85 (t, *J*= 6.8 Hz, 3H), 0.75 (ddd, *J*= 7.7 Hz, 6.7 Hz, 4.0 Hz, 1H); ^{13}C NMR δ 198.68 (C), 33.20 (CH_2), 31.86 (CH_2), 30.34 (CH), 29.05 (CH_2), 29.00 (CH_2), 25.56 (CH), 23.30 (CH_2), 22.70 (CH_2), 17.86 (CH_2), 14.95 (CH_3), 14.15 (CH_3); MS *m/z* 214 (M^+, 1), 153 (M^+-SEt, 100), 69 (C_5H_9, 49), 55 (C_4H_7, 83); HRMS calcd. for $C_{12}H_{23}OS$ 251.1464, found 251.1460; *Ee* was determined by chiral GC analysis of methyl 2-hexylcyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 80 °C for 50 min, retention times (min): 39.0 ((*R*,*R*)-enantiomer), 42.0 ((*S*,*S*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-methylcyclopropanecarbothioate (**6.34h**):
[1.0 mmol scale, 56% yield (volatile product), 87% ee, colorless oil]
$[\alpha]_D^{20}$ = −98.3 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.85 (qd, *J*= 7.4 Hz, 1.1 Hz, 2H), 1.70 (dt, *J*= 8.5 Hz, 4.3 Hz, 1H), 1.58-1.44 (m, 1H), 1.37-1.27 (m, 1H), 1.22 (td, *J*= 7.4 Hz, 1.1 Hz, 3H), 1.09 (d, *J*= 6.0 Hz, 3H), 0.74 (td, *J*= 7.2 Hz, 4.0 Hz, 1H); ^{13}C NMR δ 198.66 (C), 31.37 (CH, d, *J*= 168.4 Hz), 23.33 (CH_2, t, *J*= 141.2 Hz), 19.75 (CH, d, *J*= 169.5 Hz), 19.14 (CH_2, t, *J*= 165.2 Hz), 18.02 (CH_3, q, *J*= 126.5 Hz), 14.98 (CH_3, q, *J*= 128.0 Hz), *trans* product according to NOE; MS *m/z* 144 (M^+, 7), 83 (M^+-SEt, 100), 55 (M^+-COSEt, 29); HRMS calcd. for $C_7H_{13}OS$ 145.0682, found 145.0678; *Ee* was determined by chiral GC analysis of methyl 2-methylcyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 50 °C for 30 min, retention times (min): 8.0 ((*S*,*S*)-enantiomer), 9.8 ((*R*,*R*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-ethylcyclopropanecarbothioate (**6.34i**):
[1.0 mmol scale, 67% yield, 95% ee, colorless oil]
$[\alpha]_D^{20}$ = −109.1 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.85 (qd, *J*= 7.4 Hz, 1.5 Hz, 2H), 1.78-1.69 (m, 1H), 1.53-1.42 (m, 1H), 1.37-1.15 (m, 6H), 0.95 (t, *J*= 7.3 Hz, 3H), 0.77 (ddd, *J*= 8.0 Hz, 6.5 Hz, 4.1 Hz, 1H); ^{13}C NMR δ 198.76 (C), 30.10 (CH), 27.16 (CH), 26.32 (CH_2), 23.32 (CH_2), 17.71 (CH_2), 14.95 (CH_3), 13.21 (CH_3); MS *m/z* 158 (M^+, 8), 97 (M^+-SEt, 100), 55 (C_4H_7, 92); HRMS calcd. for $C_8H_{15}OS$ 159.0838, found 159.0835; *Ee* was determined by chiral GC analysis of methyl 2-ethylcyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 50 °C for 30 min, 50 °C to 140 °C in 18 min, retention times (min): 41.0 ((*S*,*S*)-enantiomer), 41.6 ((*R*,*R*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-isopropylcyclopropanecarbothioate (**6.34j**):
[1.0 mmol scale, 89% yield, 70% ee, colorless oil]
$[\alpha]_D^{20}$ = −77.4 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.92-2.76 (m, 2H), 1.75 (dt, *J*= 8.4 Hz, 4.3 Hz, 1H), 1.36-1.24 (m, 2H), 1.24-1.17 (m, 3H), 1.09-0.98 (m, 1H), 0.98-0.91 (m, 6H), 0.78 (ddd, *J*= 6.2 Hz, 4.7 Hz, 2.1 Hz, 1H); ^{13}C NMR δ 198.65 (C), 33.20 (CH), 32.36 (CH), 29.48 (CH), 23.28 (CH_2), 21.81 (CH_3), 21.57 (CH_3), 16.84 (CH_2), 14.91 (CH_3); MS *m/z* 172 (M^+, 4), 111 (M^+-SEt, 57), 69 (C_5H_9, 49), 55 (C_4H_7, 100); HRMS calcd. for $C_9H_{17}OS$ 173.0995, found 173.0989; *Ee* was determined by chiral GC analysis of methyl 2-isopropylcyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 80 °C for 50 min, retention times (min): 10.4 ((*R*,*R*)-enantiomer), 11.8 ((*S*,*S*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-isobutylcyclopropanecarbothioate (**6.34k**):
[1.0 mmol scale, 91% yield, 84% ee, colorless oil]
$[\alpha]_D^{20}$ = −114.0 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.84 (qd, *J*= 7.4 Hz, 1.4 Hz, 2H), 1.75-1.59 (m, 2H), 1.53-1.41 (m, 1H), 1.36-1.28 (m, 1H), 1.25-1.13 (m, 5H), 0.94-0.85 (m, 6H), 0.73 (ddd, *J*= 7.9 Hz, 6.5 Hz, 4.0 Hz, 1H);^{13}C NMR δ 198.63 (C), 42.35 (CH_2), 30.43 (CH), 28.52 (CH), 23.96 (CH), 23.30 (CH_2), 22.58 (CH_3), 22.51 (CH_3), 17.87 (CH_2), 14.94 (CH_3); MS *m/z* 186 (M^+, 1), 125 (M^+-SEt, 92), 97 (M^+-COSEt, 29), 55 (C_4H_7, 100); HRMS calcd. for $C_{10}H_{19}OS$ 187.1151, found 187.1148; *Ee* was determined by chiral GC analysis of methyl 2-isobutylcyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 70 °C for 50 min, retention times (min): 12.8 ((*R*,*R*)-enantiomer), 14.4 ((*S*,*S*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-(but-3-enyl)cyclopropanecarbothioate (**6.34l**):
[3.0 mmol scale, 88% yield, 94% ee, colorless oil]
$[\alpha]_D^{20}$ = −111.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 5.88-5.46 (m, 1H), 5.08-4.64 (m, 2H), 2.76 (qd, *J*= 7.4 Hz, 1.9 Hz, 2H), 2.25-1.84 (m, 2H), 1.78-1.55 (m, 1H), 1.40 (dddd, *J*= 13.5 Hz, 8.1 Hz, 3.8 Hz, 2.0 Hz, 1H), 1.37-1.27 (m, 2H), 1.23 (tdd, *J*= 6.0 Hz, 4.5 Hz, 1.7 Hz, 1H), 1.18-1.07 (m, 3H), 0.74-0.63 (m, 1H); ^{13}C NMR δ 197.84 (C), 137.57 (CH), 114.91 (CH_2), 33.10 (CH_2), 32.40 (CH_2), 29.94 (CH), 24.66 (CH), 23.03 (CH_2), 17.42 (CH_2), 14.77 (CH_3); MS *m/z* 184 (M^+, 2), 123 (M^+-SEt, 100), 95 (M^+-COSEt, 48), 55 (C_4H_7, 79); HRMS calcd. for $C_{10}H_{17}OS$ 185.0995, found 185.0991; *Ee* was determined by chiral GC analysis of methyl 2-(but-3-enyl)cyclopropanecarboxylate,[xi] column: Chiraldex-G-TA, 70 °C for 50 min, retention times (min): 17.4 ((*R*,*R*)-enantiomer), 19.8 ((*S*,*S*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-phenethylcyclopropanecarbothioate (**6.34g**):
[1.0 mmol scale, 97% yield, 84% ee, colorless oil]
$[\alpha]_D^{20}$ = −101.7 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 7.36-7.28 (m, 2H), 7.27-7.18 (m, 3H), 2.92 (q, *J*= 7.5 Hz, 2H), 2.75 (t, *J*= 7.5 Hz, 2H), 1.81 (dt, *J*= 8.3 Hz, 4.2 Hz, 2H), 1.75-1.53 (m, 3H), 1.39 (dt, *J*= 8.6 Hz, 4.3 Hz, 1H), 1.29 (t, *J*= 7.4 Hz, 3H), 0.82 (ddd, *J*= 8.0 Hz, 6.3 Hz, 4.1 Hz, 1H); ^{13}C NMR δ 198.39 (C), 141.53 (C), 128.43 (CH), 128.40 (CH), 125.92 (CH), 35.38 (CH_2), 35.04 (CH_2), 30.20 (CH), 24.91 (CH), 23.29 (CH_2), 17.71 (CH_2), 14.96 (CH_3); MS *m/z* 234 (M^+, 1), 173 (M^+-SEt, 42), 129 (C_6H_9OS, 100), 91 (C_7H_7, 78); HRMS calcd. for $C_{14}H_{19}OS$ 235.1151, found 235.1136; *Ee* was determined by chiral HPLC analysis of methyl 3-(chloromethyl)-5-phenylpentanoate (vide supra),[xi] column: chiralcel OB-H, (99:1 heptane:*i*PrOH); retention times (min): 26.0 (*S*-enantiomer (corresponds with the (1*R*,2*R*)-enantiomer), 32.7 (*R*-enantiomer (corresponds with the (1*S*,2*S*)-enantiomer)).

(1*R*,2*R*)-methyl 2-phenethylcyclopropanecarboxylate (**6.34e**):
1) Prepared via the general procedure for the Cu-catalyzed 1,4-addition of Grignard reagent to 4-chlorocrotonates leading to 4-chloro 3-substituted butenoates.
[0.5 mmol scale, 65% yield (traces of open product), >95% ee]
2) Prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to *trans* 2-substituted cyclopropanecarbothioates.
[1.0 mmol scale, 68% yield, >95% ee, colorless oil]
$[\alpha]_D^{20}$ = −82.8 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 7.34-7.27 (m, 2H), 7.25-7.17 (m, 3H), 3.69 (s, 3H), 2.80-2.71 (m, 2H), 1.65 (dd, *J*= 15.1 Hz, 7.3 Hz, 2H), 1.50-1.36 (m, 2H), 1.25-1.17 (m, 1H), 0.73 (ddd, *J*= 8.1 Hz, 6.4 Hz, 4.2 Hz, 1H); ^{13}C NMR δ 174.78 (C), 141.68 (C), 128.44 (CH), 128.38 (CH), 125.91 (CH), 51.62 (CH_2), 35.50 (CH), 35.04 (CH), 22.62 (CH_2), 20.12 (CH_2), 15.51 (CH_2); MS *m/z* 173 (M^+-OMe, 1), 130 ($C_{10}H_{10}$, 84), 117 (C_9H_9, 28), 105 (C_7H_7, 35), 91 (C_7H_7, 100); HRMS calcd. for $C_{13}H_{17}O_2$ 205.1223, found 205.1209; *Ee* was determined by chiral HPLC analysis, column: chiralcel OB-H, (99:1 heptane:*i*PrOH); retention times (min): 24.7 (1*R*,2*R*-enantiomer), 25.3 (1*S*,2*S*)-enantiomer).

1-((1*R*,2*R*)-2-methylcyclopropyl)dodecan-1-one (**6.34m**):
prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates.
[1.0 mmol scale, 87% yield, 98% ee, colorless oil (turning into a white solid after storage at −20 °C, with mp around 20 °C)]
$[\alpha]_D^{20}$ = −70.1 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.46 (t, *J*= 7.5 Hz, 2H), 1.59 (ddd, *J*= 23.6 Hz, 11.1 Hz, 5.6 Hz, 3H), 1.37-1.15 (m, 17H), 1.06 (d, *J*= 6.0 Hz, 3H), 0.84 (t, *J*= 6.8 Hz, 3H), 0.64 (ddd, *J*= 7.8 Hz, 6.4 Hz, 3.5 Hz, 1H); ^{13}C NMR δ 210.62 (C), 43.74 (CH_2), 31.99 (CH_2), 29.69 (2x CH_2), 29.57 (CH_2), 29.54 (CH), 29.51(CH_2), 29.41 (CH_2), 29.36 (CH_2), 24.18 (CH_2), 22.75 (CH_2), 19.87 (CH), 19.12 (CH_2), 18.17 (CH_3), 14.16 (CH_3); MS *m/z* 238 (M^+, 2), 111 ($C_7H_{11}O$, 15), 98 ($C_6H_{10}O$, 100), 83 (C_5H_7O, 15), 55 (C_4H_7, 27); HRMS calcd. for $C_{16}H_{31}O$ 239.2369, found 239.2351; *Ee* was determined by chiral GC analysis, column: Chiralsil-Dex-CB, 50 °C to 140 °C in 9 min, 140 °C for 50 min, 140 °C to 160 °C in 10 min; retention times (min): 62.9 ((1*R*,2*R*)-enantiomer), 64.4 ((1*S*,2*S*)-enantiomer).

1-((1*R*,2*R*)-2-phenethylcyclopropyl)dodecan-1-one (**6.34b**):
prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates,
[1.0 mmol scale, 75% yield, 96% ee, colorless oil (turning into a white solid after storage at −20 °C, with mp around 20 °C)]
$[\alpha]_D^{20}$ = −73.8 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 7.34-7.26 (m, 2H), 7.25-7.16 (m, 3H), 2.83-2.63 (m, 3H), 2.48-2.38 (m, 2H), 1.74 (ddd, *J*= 14.4 Hz, 10.3 Hz, 4.1 Hz, 1H), 1.67-1.52 (m, 4H), 1.49-1.20 (m, 17H), 0.93 (t, *J*= 6.8 Hz, 3H), 0.72 (ddd, *J*= 7.8 Hz, 6.4 Hz, 3.7 Hz, 1H); ^{13}C NMR δ 210.46 (C), 141.70 (C), 128.46 (CH), 128.40 (CH), 125.91 (CH), 43.60 (CH_2), 35.65 (CH_2), 35.18 (CH_2), 31.99 (CH_2), 29.71 (CH_2), 29.70 (CH_2), 29.58 (CH_2), 29.52 (CH_2), 29.43 (CH_2), 29.36 (CH_2), 28.50 (CH), 25.19 (CH), 24.10 (CH_2), 22.77 (CH_2), 17.53 (CH_3), 14.20 (CH_3); MS *m/z* 328 (M^+, 1), 130 ($C_{10}H_{10}$, 100), 91 (C_7H_7, 25); HRMS calcd. for $C_{23}H_{37}O$ 329.2839, found 329.2816; *Ee* was determined by chiral HPLC analysis, column: chiralcel OJ-H, (99:1 heptane:*i*PrOH); retention times (min): 12.1 (1*R*,2*R*-addition product), 13.3 (1*S*,2*S*)-enantiomer).

Formal syntheses of cascarillic acid (**6.36**): Synthesis of (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde (**6.35c**)

General procedure for the reduction of the thioester to an aldehyde:
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the thioester (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (2.5 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to −78 °C and DIBAL-H (1.2 equiv) was added dropwise. The reaction mixture was stirred for 3 h at −78 °C. Subsequently the reaction mixture was poured into a roundbottom flask with aq Rochelle's salt-solution (saturated, 5 mL/mmol substrate), stirred for 1 h at rt and the layers were

separated. After extraction with CH_2Cl_2 (2x 5 mL/mmol substrate), the combined organic extracts were washed with the aq Rochelle's salt solution (2x 5 mL/mmol substrate), dried and carefully concentrated. Flash column chromatography (5:95 Et_2O:pentane) yielded the pure product.

(1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde (**6.35c**):
[0.5 mmol scale, 83% yield, colorless oil]
$[\alpha]_D^{20}$ = −36.9 (c=1.0, CH_2Cl_2), Literature value:[21] $[\alpha]_D^{20}$= −26.0 (c=0.35, CH_2Cl_2) for the (1*R*,2*R*)-enantiomer.
Experimental data in accordance with data reported in ref 21.

Formal synthesis of grenadamide (**6.37**): Synthesis of (1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde (**6.35n**)
(1*R*,2*R*)-S-ethyl 2-heptylcyclopropanecarbothioate **6.34n** was prepared according to the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction of Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates.
[1.0 mmol scale, 84% yield, 95% ee, colorless oil]
$[\alpha]_D^{20}$ = −107.9 (c=1.0, CH_2Cl_2); ^{1}H NMR δ 2.84 (qd, *J*= 7.4 Hz, 1.0 Hz, 2H), 1.71 (dt, *J*= 8.2 Hz, 4.3 Hz, 1H), 1.54-1.14 (m, 17H), 0.84 (t, *J*= 6.8 Hz, 3H), 0.74 (ddd, *J*= 7.9 Hz, 6.6 Hz, 4.0 Hz, 1H); ^{13}C NMR δ 198.59 (C), 33.20 (CH_2), 31.90 (CH_2), 30.32 (CH), 29.31 (CH_2), 29.29 (CH_2), 29.08 (CH_2), 25.51 (CH), 23.28 (CH_2), 22.72 (CH_2), 17.81 (CH_2), 14.93 (CH_3), 14.15 (CH_3); MS *m/z* 228 (M^+, 1), 167 (M^+-SEt, 92), 69 (C_5H_9, 38), 55 (C_4H_7, 93); HRMS calcd. for $C_{13}H_{25}OS$ 229.1621, found 229.1618; *Ee* was determined by chiral GC analysis for methyl 2-heptylcyclopropanoate,[xi] column: Chiraldex-G-TA, 85 °C for 50 min, 85 °C to 180 °C in 9.5 min, retention times (min): 53.0 ((*R*,*R*)-enantiomer), 53.6 ((*S*,*S*)-enantiomer).

(1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde (**6.35n**) was prepared according to the general procedure for the reduction of the thioester to an aldehyde.
[0.5 mmol scale, 84% yield, colorless oil]
$[\alpha]_D^{20}$ = −43.9 (c=1.0, $CHCl_3$), Literature value:[24] $[\alpha]_D^{20}$ = +41.4 (c=1.45, $CHCl_3$) for the *trans* (1*S*,2*S*)-enantiomer.
Experimental data in accordance with data reported in ref 24.

Attempted synthesis of Majusculoic acid:
E-2-(*E*-hex-2-en-1-ylidene)-1,1-dimethylhydrazine (**6.42**) was prepared according to ref 28.
In a roundbottom flask equipped with septum and stirring bar, the aldehyde (1 equiv) is dissolved in CH_2Cl_2 (10 mL/mmol substrate). Then 1,1-dimethylhydrazine (1.05 equiv) is added. The reaction mixture is stirred for 40 h. Subsequently the reaction is diluted with water (10 mL/mmol substrate). After separation and extraction with CH_2Cl_2 (1x 10 mL/mmol substrate), the combined organic extracts were dried with Na_2SO_4 and carefully concentrated to a yellow oil.
[40 mmol scale, 89% yield, yellow oil]
Experimental data in accordance with data reported in ref 28.

2-(*Z*-3-bromohex-2-enylidene)-1,1-dimethylhydrazine (**6.43**):[29]
In a dried roundbottom flask equipped with septum and stirring bar under a N_2 atmosphere the substrate (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4 mL/mmol substrate) and cooled to −20 °C. Then bromine (1.05 equiv) and triethylamine (1.05 equiv) were added dropwise. The reaction mixture is stirred for 1 h at −20 °C and for 1 h at −10 °C. Subsequently the reaction mixture is diluted with water (10 mL/mmol substrate). After separation and extraction with CH_2Cl_2 (1x 10 mL/mmol substrate), the combined organic extracts were dried with Na_2SO_4 and carefully concentrated to a yellow oil. Flash column chromatography (gradient 2:98 to 5:95 Et_2O:pentane) yielded a mixture of the *E*- and *Z*-product.
[30 mmol scale, 49% yield, *Z*:*E* 8:1, colorless oil]

^{1}H NMR δ 7.04 (d, *J*= 8.3 Hz, 1H), 6.38 (dd, *J*= 8.3 Hz, 1.0 Hz, 1H), 2.87 (d, *J*= 1.9 Hz, 6H), 2.45 (t, *J*= 7.2 Hz, 2H), 1.64-1.52 (m, 2H), 0.87 (td, *J*= 7.4, 2.2 Hz, 3H). Residual peaks *E*-enantiomer: 6.90 (d, *J*= 9.1 Hz, 1H), 6.59 (d, *J*= 9.1 Hz, 1H), 2.84 (d, *J*= 1.9 Hz, 6H), 2.57-2.51 (m, 2H). ^{13}C NMR δ 132.94 (CH), 127.95 (C), 126.30 (CH), 43.80 (CH_2), 42.63 (CH_3), 42.60 (CH_3), 21.40 (CH_2), 12.97 (CH_3). Residual peaks *E*-enantiomer: 131.23 (CH), 129.19 (CH), 38.26 (CH_2), 13.08 (CH_3); MS *m/z* 220 (M^+[^{81}Br], 37), 218 (M^+[^{79}Br], 37), 139 (M^+-Br, 43), 110 (M^+-Br-Et, 79), 95 (M^+-Br-NMe_2, 100); HRMS calcd. for $C_8H_{16}{}^{79}BrN_2$ 219.0491, found 219.0485, calcd. for $C_8H_{16}{}^{81}BrN_2$ 221.0471, found 221.0463.

Z-3-bromohex-2-enal **6.44**:[30]
In a roundbottom flask equipped with septum and stirring bar the substrate (1.0 equiv) was dissolved in 1 M HCl (aq 10 mL/mmol substrate) and stirred for 5 min. Then pentane (10 mL/mmol) was added. The reaction mixture was stirred vigorously for 16 h. Subsequently the layers were separated and the aqueous layer was extracted with pentane (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 4:96 Et_2O:pentane) afforded the pure *Z*-product.
[12.5 mmol scale, 67% yield, pure *Z*-product, colorless oil]
^{1}H-NMR spectrum in accordance with ref 47.
^{1}H NMR δ 9.82 (dd, *J*= 6.7 Hz, 0.6 Hz, 1H), 6.24 (dt, *J*= 6.7 Hz, 0.9 Hz, 1H), 2.65-2.53 (m, 2H), 1.71-1.57 (m, 2H), 0.91 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR δ 193.44 (C), 150.49 (CH), 128.10 (C), 44.94 (CH_2), 21.01 (CH_2), 12.87 (CH_3); MS *m/z* 178 (M^+[^{81}Br], 9), 176 (M^+[^{79}Br], 9), 97 (M^+-Br, 100), 69 (C_5H_9, 37), 67 (C_4H_3O, 48), 53 (C_4H_5, 35); HRMS calcd. for $C_6H_9{}^{79}BrONa$ 198.9729, found 198.9724, calcd. for $C_6H_9{}^{81}BrONa$ 200.9709, found 200.9704.

Z-4-bromohepta-1,3-diene **6.40**:[31]
In a roundbottom flask equipped with septum and stirring bar under a N_2 atmosphere methyltriphenylphosphonium bromide (1.5 equiv) was dissolved in anhydrous THF (10 mL/mmol substrate). The reaction mixture was cooled to 0 °C and *n*BuLi (1.4 equiv) was added. After stirring for 1 h the substrate (1.0 equiv) was added. After 30 min the reaction mixture was quenched with water (10 mL/mmol substrate). Subsequently the reaction mixture was extracted with Et_2O (3x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:99 Et_2O:pentane) afforded the pure product.
[11.6 mmol scale, 73% yield, colorless oil]
^{1}H NMR δ 6.62 (dt, *J*= 17.0 Hz, 10.1 Hz, 1H), 6.27 (ddd, *J*= 9.9 Hz, 1.8 Hz, 0.9 Hz, 1H), 5.36-5.26 (m, 1H), 5.25-5.15 (m, 1H), 2.47 (t, *J*= 7.3 Hz, 2H), 1.69-1.53 (m, 2H), 0.99-0.82 (m, 3H); ^{13}C NMR δ 134.79 (CH), 130.07 (C), 128.39 (CH), 118.99 (CH_2), 43.84 (CH_2), 21.52 (CH_2), 13.08 (CH_3); MS *m/z* 176 (M^+[^{81}Br], 30), 174 (M^+[^{79}Br], 34), 95 (M^+-Br, 94), 67 (C_5H_7, 100), 65 (C_5H_5, 90); HRMS calcd. for $C_7H_{12}{}^{79}Br$ 175.0117, found 174.9750, calcd. for $C_7H_{11}{}^{81}BrNa$ 177.0096, found 176.9904.

(1*R*,2*R*)-S-ethyl 2-(3*E*,5*Z*-6-bromonona-3,5-dienyl)cyclopropanecarbothioate **6.45**:[32]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere Hoveyda-Grubbs II catalyst (5.0 mol%) and 2,6-dichlorobenzoquinone (10.0 mol%) were dissolved in anhydrous CH_2Cl_2 (8.0 mL/mmol substrate). After stirring for 2 min, a mixture of both the substrate (1.0 equiv) and the terminal alkene (2.7 equiv) dissolved in anhydrous CH_2Cl_2 (1.0 mL/mmol substrate) were added. Then a reflux condenser under a N_2 atmosphere was placed on the Schlenk tube and the mixture was refluxed for 16 h. The reaction mixture was subsequently quenched with ethyl vinyl ether (1.0 mL/mmol substrate) and stirred for 10 min. Subsequently the reaction mixture was concentrated to a brown oil. Flash column chromatography (gradient pentane to 1:99 Et_2O:pentane) afforded a mixture of the product, **6.34l** and traces of an unidentified side product which was used for the next step.
[3.34 mmol scale, ~80% conversion, ~50% yield, yellow oil][xii]

[xii] Optical rotation and MS were not measured before the intermediates had degraded.

^{1}H NMR δ 6.35-6.13 (m, 2H), 5.87-5.67 (m, 1H), 2.95-2.70 (m, 2H), 2.38 (t, *J*= 7.2 Hz, 2H), 2.27-2.04 (m, 2H), 1.78-1.66 (m, 1H), 1.62-1.24 (m, 6H), 1.19 (t, *J*= 7.4 Hz, 3H), 0.95-0.82 (m, 3H), 0.75 (ddd, *J*= 8.0, 6.2, 4.1 Hz, 1H); ^{13}C NMR δ 198.12 (C), 135.45 (CH), 128.62 (CH), 127.61 (CH), 127.21 (C), 43.58 (CH_2), 32.73 (CH_2), 32.36 (CH_2), 30.14 (CH), 24.78 (CH), 23.23 (CH_2), 21.42 (CH_2), 17.53 (CH_2), 14.86 (CH_3), 12.95 (CH_3); HRMS calcd. for $C_{15}H_{23}{}^{79}BrOSNa$ 353.0545, found 353.0530, calcd. for $C_{15}H_{23}{}^{81}BrOSNa$ 355.0525, found 355.0510.

(1*R*,2*R*)-2-(3*E*,5*Z*-6-bromonona-3,5-dienyl)cyclopropanecarbaldehyde (**6.46**) was prepared according to the general procedure for the reduction of the thioester to an aldehyde, 1 h reaction time, Flash column chromatography (gradient hexane to 10:90 Et_2O:hexane) afforded a mixture of the product, the corresponding aldehyde of **6.34l** and traces of an unidentified side product which was used for the next step.
[~3.0 mmol scale, colorless oil]

E-ethyl 3-((1*R*,2*R*)-2-(3*E*,5*Z*-6-bromonona-3,5-dienyl)cyclopropyl)acrylate (**6.47**):[34]
In a roundbottom flask equipped with stirring bar under a N_2 atmosphere, NaH (60% dispersion in mineral oil, 1.75 equiv) was vigorously stirred in anhydrous THF (1.0 mL/mmol aldehyde) and cooled to 0 °C. Triethyl phosphonoacetate (1.75 equiv) was added dropwise and the mixture was stirred for 30 min and cooled to −20 °C. Subsequently, the aldehyde (1 equiv) dissolved in anhydrous THF (0.1 mL/mmol aldehyde), was added dropwise. After addition, the solution was stirred for 20 min at −20 °C and was subsequently stirred at rt for 30 min. The reaction mixture was diluted with Et_2O (2.0 mmol/mmol aldehyde) and the solution was subsequently washed with NH_4Cl (saturated aq solution, 2.0 mL/mmol aldehyde), Na_2CO_3 (saturated aq solution, 2.0 mL/mmol aldehyde) and brine (2.0 mL/mmol aldehyde). The combined organic extracts were dried and concentrated. Flash column chromatography (gradient hexane 5:95 Et_2O:hexane) yielded the pure product and traces of an unidentified side product.
[~3.0 mmol scale, 20% yield (3 steps), yellowish oil][xii]
^{1}H NMR δ 6.53-6.39 (m, 1H), 6.28 (dd, *J*= 15.1 Hz, 9.8 Hz, 1H), 6.18 (d, *J*= 9.9 Hz, 1H), 5.85-5.71 (m, 2H), 4.14 (q, *J*= 7.1 Hz, 2H), 2.41 (t, *J*= 7.2 Hz, 2H), 2.19 (dd, *J*= 14.7 Hz, 7.3 Hz, 2H), 1.68-1.50 (m, 2H), 1.50-1.16 (m, 6H), 1.01 (tdd, *J*= 8.9 Hz, 6.6 Hz, 2.6 Hz, 1H), 0.94-0.71 (m, 5H); ^{13}C NMR δ 166.81 (C), 153.27 (CH), 135.90 (CH), 128.61 (CH), 127.69 (CH), 127.33 (C), 117.87 (CH), 60.02 (CH_2), 43.70 (CH_2), 33.29 (CH_2), 32.62 (CH_2), 22.83 (CH), 22.25 (CH), 21.53 (CH_2), 16.02 (CH_2), 14.40 (CH_3), 13.04 (CH_3); HRMS calcd. for $C_{17}H_{25}{}^{79}BrO_2Na$ 363.0930, found 363.0914, calcd. for $C_{17}H_{25}{}^{81}BrO_2Na$ 365.0910, found 365.0896.

Synthesis of 2-chlorooctanal (**6.57a**):[38]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere the substrate (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (2.0 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and L-proline (0.1 equiv, low ee expected: 23% ee was obtained for the chlorination of 3-methylbutanal using this catalyst[38]) and NCS (1.3 equiv) were added. After stirring for 1 h (completion) pentane was added to the solution and the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract was dried and concentrated to a yellow oil. Extraction with pentane yielded the product as a colorless oil.
[10.0 mmol scale, crude reaction mixture was used for the synthesis of *E*-S-ethyl 4-chlorodec-2-enethioate, colorless oil]

General procedure for the Wittig reaction of 2-chloroalkenals to synthesize 4-chloro α,β-unsaturated thioesters:[44]
In a dried round two necked flask equipped with septum and cooler under a N_2 atmosphere, the Wittig reagent $Ph_3PCHCOSEt$ (1.3 equiv) was dissolved in anhydrous CH_2Cl_2 (6 mL/mmol substrate). To this solution the substrate (1.0 equiv) was added. After stirring for 16 h at 40 °C the CH_2Cl_2 was evaporated and pentane was added. The mixture was filtered and evaporated to a suspension. Flash column chromatography (gradient Et_2O:pentane 1:99 to 3:97) yielded the product as a colorless oil.

Racemic *E*-S-ethyl 4-chlorodec-2-enethioate (**6.59a**) was prepared according to the general procedure for the Wittig reaction of 2-chloroalkenals to synthesize 4-chloro α,β-unsaturated thioesters.
[5.0 mmol scale, 77% yield (2 steps), colorless oil]
^{1}H NMR δ 6.78 (dd, *J*= 15.3 Hz, 7.6 Hz, 2H), 6.25 (dd, *J*= 15.3 Hz, 1.1 Hz, 1H), 4.41 (q, *J*= 6.6 Hz, 1H), 2.95 (q, *J*= 7.4 Hz, 2H), 1.83 (q, *J*= 7.5 Hz, 2H), 1.50-1.20 (m, 11H), 0.86 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR δ 189.64 (C), 141.87 (CH), 128.90 (CH), 60.08 (CH), 37.82 (CH_2), 31.66 (CH_2), 28.73 (CH_2), 26.26 (CH_2), 23.48 (CH_2), 22.62 (CH_2), 14.76 (CH_3), 14.12 (CH_3); MS *m/z* 250 (M^+[^{37}Cl], 1), 248 (M^+[^{35}Cl], 2), 189 (M^+[^{37}Cl]-SEt, 23), 187 (M^+[^{35}Cl]-SEt, 72), 81 (C_5H_5O, 100), 67 (C_4H_3O, 41), 55 (C_3H_3O, 64); HRMS calcd. for $C_{12}H_{22}ClOS$ 249.1074, found 249.1073.

Synthesis of 2-chloro-3-phenylpropanal (**6.57b**):[38]
In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (2.0 mL/mmol substrate). After 5 min stirring at rt the mixture was cooled to 0 °C and racemic proline (0.5 equiv) and NCS (1.5 equiv) were added. After stirring for 5 h (completion) pentane was added and the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract was dried and concentrated to a yellow oil. Extraction with pentane yielded the product as a colorless oil. Flash column chromatography (Et_2O:pentane 5:95) yielded the pure aldehyde.

2-Chloro-3-phenylpropanal (**6.57b**); data in accordance with data described in ref 38.
[5.0 mmol scale, 47% yield, colorless oil]
MS *m/z* 168 (M^+, 1), 133 (M^+-Cl, 76), 91 (C_7H_7, 100); HRMS calcd. for C_9H_9ClONa 191.0234, found 191.0227.

E-S-ethyl 4-chloro-5-phenylpent-2-enethioate (**6.59b**) was prepared according to the general procedure for the Wittig reaction of 2-chloroalkenals to synthesize 4-chloro α,β-unsaturated thioesters.
[2.2 mmol scale, 75% yield, colorless oil]
^{1}H NMR δ 7.39-7.16 (m, 5H), 6.85 (ddd, *J*= 15.2 Hz, 7.5 Hz, 1.1 Hz, 1H), 6.23 (dt, *J*= 15.2 Hz, 1.1 Hz, 1H), 4.63 (dt, *J*= 8.2 Hz, 7.1 Hz, 1H), 3.16 (d, *J*= 7.1 Hz, 2H), 2.97 (qd, *J*= 7.4 Hz, 1.0 Hz, 2H), 1.29 (td, *J*= 7.4 Hz, 1.1 Hz, 3H); ^{13}C NMR δ 189.47 (C), 140.87 (CH), 136.23 (C), 129.51 (CH), 129.48 (CH), 128.64 (CH), 127.31 (CH), 60.21 (CH), 44.32 (CH_2), 23.48 (CH_2), 14.70 (CH_3); MS *m/z* 219 (M^+-Cl, 2), 157 (M^+-Cl-SEt, 23), 129 (C_6H_9OS, 40), 128 (C_6H_8OS, 30), 91 (C_7H_7, 100); HRMS calcd. for $C_{13}H_{16}ClOS$ 255.0605, found 255.0598.

6.13 References and notes

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Chapter 7

Cu-Catalyzed Asymmetric Allylic Alkylation and Conjugate Addition using Grignard reagents: Perspectives and Future Prospects

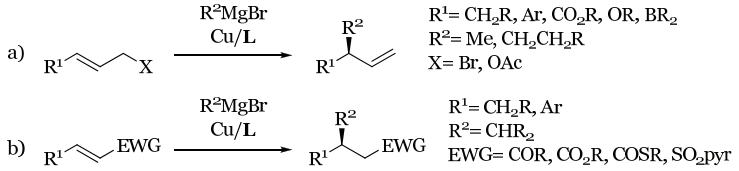
In this chapter the current scope for the Cu-catalyzed asymmetric allylic alkylation and conjugate addition using Grignard reagents with respect to substrates and Grignard reagents is summarized. Furthermore, the potential application of these transformations in industry is discussed. Finally, some future directions for studies to expand the potential of these asymmetric Cu-catalyzed transformations are suggested.

7.1 Current scope of asymmetric allylic alkylation and conjugate addition with Grignard reagents

As described in chapter 1, multiple breakthroughs have been achieved in ACA and AAA using Grignard reagents.[1] Currently, the scope of the AAA with Grignard reagents[1] includes aliphatic[2] and aromatic[2a,b,c,d,h,i] allylic substrates with primary halogens as leaving groups (Figure 7.1a). Furthermore, when at least one CH_2 unit is present in between the reaction site (γ-position) and functionality, a large variety of functionalized[2e,h,i] allylic substrates can be used. Finally, allylic substrates with a functional group directly attached to the reaction site can be selectively transformed using Grignard reagents when the γ-position is substituted by an ester[3] (see chapter 5), oxygen[4] or boron[5] substituent (in the so-called *h*AAA). With respect to the Grignard reagents, aliphatic organomagnesium reagents,[2,3,4,5] as well as aryl[6] Grignard reagents can be used to obtain S_N2' products in excellent yields, regio- and enantioselectivities (up to 99% regio- and enantioselectivity). Furthermore, when at least two CH_2 units are incorporated in between reaction site and functionality, functionalized Grignard reagents can be used. The ligands of choice for AAA are TaniaPhos, [2h,i,3,4] several phosphoramidites[2a,b,c,d,e,f,5] and N-heterocyclic carbenes.[6]

The scope of the ACA of Grignard reagents[1] includes cyclic[7] and acyclic[8] ketones, esters[9] (including multiple unsaturated esters and thioesters,[10] see chapter 2 to 4), lactones,[7] thioesters[11] and sulfones[12] as substrates (Figure 7.1b). These Michael acceptors can have aliphatic or aromatic substituents at the β-position, as well as other functional groups when at least one CH_2 unit separates reaction site and functionality. Ligands of choice for the addition of aliphatic, branched (no spacer required) and functionalized (incorporating at least two CH_2 spacers between reaction site and functionality) alkyl Grignard reagents are Tol-BINAP[9b,c,11b,12] and several ferrocenyl ligands; including JosiPhos[7,8,9a,11a] and reversed JosiPhos.[9,10]

Figure 7.1. *Current scope of AAA (a) and ACA (b).*



7.2 Potential use of asymmetric conjugate addition and allylic alkylation in industry

Asymmetric synthesis of molecules is required in the pharmaceutical and related specialty and fine chemical industries and is typically conducted in small- to medium-scale processes.[13] Although academic research is not primarily directed to develop methods for the industrial production of chemicals, it is interesting to consider what aspects of a methodology should be improved to make it a viable alternative for industry. For the construction of asymmetric carbon centers with at least two non-functionalized alkyl side chains, ACA and AAA[1] will have to compete with mainly two other synthetic methods, the intensively studied asymmetric

hydrogenation[14] which in several cases is also developed into an industrial process, based on rhodium,[14a,b] ruthenium[14a,b] and iridium[14a,c] catalysts, and Cu-catalyzed conjugate reduction.[15] Furthermore, enzymatic reduction by reductases[16] is an alternative.

Comparison of the synthetic methods for industrial use is highly dependent on the availability or, if required, on the synthesis of the required starting materials and thus a fair in-depth comparison of these methods is difficult to make. However, in general the control of the olefin geometry for 1,1,2-trisubstituted olefins in either Wittig-type reactions or cross metathesis reactions is challenging. This is a key issue for asymmetric hydrogenation and conjugate reduction as trisubstituted olefins are required for these transformations, in contrast to the 1,2-disubstituted olefin starting materials used in ACA and AAA.

In the remainder of this paragraph we will focus on desired improvements for ACA and AAA to allow the use of these synthetic methodologies in industry. It should be noted however, that several aspects of the ACA and AAA methods do not need any further improvement for potential industrial use. First of all, in spite of the highly exothermic reactions of Grignard reagents with water, safe handling of these reagents in industry is possible.[17] Furthermore, although non-inorganic salts are preferred in industry with respect to their disposal, the bromide and chloride leaving groups in AAA do not pose severe problems. Finally, *t*BuOMe, one of the solvents of choice for ACA, is one of the preferred solvents in industry. However, the use of CH_2Cl_2 as solvent in industry is not preferred.

The low temperature employed in both ACA and AAA (−78 °C and in some cases to a maximum of −20 °C) is the main drawback for use of ACA and AAA in industry. With respect to costs for industrial processes −40 °C is the lowest temperature considered to be acceptable, while 0 °C is a more preferred temperature. Another important consideration for use of a catalytic method in industry is the price of the catalyst, the required catalyst loading and turnover numbers (TON) and turnover frequencies (TOF) for a catalyst. Copper is one of the less expensive metals,[i] especially compared to rhodium, ruthenium and iridium. However, the price of the catalyst is also highly dependent on the ligand and N-heterocyclic carbene ligands, JosiPhos, TaniaPhos and related ferrocenyl ligands are relatively expensive ligands and can are currently almost exclusively used for the preparation of high value products.[ii] In contrast, Tol-BINAP and 'simple'[iii] phosphoramidites are less expensive. With respect to catalyst loading, a 1% catalyst loading allows both ACA and AAA to proceed in a highly chemo-, regio- and enantioselective way. In view of the absence of data studies are needed to determine if a further decrease of catalyst loading is possible. Finally, although ACA and AAA reactions are typically fast,[iv] no turn-over numbers and frequencies have been reported up till now. Another aspect of the catalysts which has only scarcely been studied is the stability and possible

[i] www.infomine.com data 7th of april 2010: Cu: 8 USD/kg, Rh: 95000 USD/kg, Ru: 1000 USD/kg, Ir: 16500 USD/kg.

[ii] The synthesis of an intermediate for the herbicide (*S*)-metolachlor using JosiPhos by Syngenta/Solvias is a striking exception (see ref 13, p. 313).

[iii] A nonsubstituted BINOL or biphenyl-backbone with a cheap amine gives the simplest and least expensive phosphoramidites. A typical example is MonoPhos®. Of course depending on the product more complicated phosphoramidites can be used in industry.

[iv] According to TLC, ACA and AAA are in many cases complete as soon as addition of substrate to the reaction mixture is finished.

recycling of the catalyst. For ACA with JosiPhos as ligand, catalyst recycling is known to be possible.[9a] However, exact data on the percentage of catalyst recovery, as well as possible deactivation of the catalyst are unknown.

As can be concluded from the considerations in this paragraph, up till know, the use of the ACA method based on Tol-BINAP catalyst[9b,c,11b,12] is best suited for potential use in industry. Further research to make ACA and AAA with Grignard reagents more cost-efficient should be directed towards allowing the reactions to be performed at higher temperatures (0 °C to ambient temperature) with good selectivity and yield. Furthermore, studies on the reaction with lower catalyst loading, on the TOF and TON and on the possible recycling of the catalyst should be performed.

7.3 Novel substrates for asymmetric conjugate addition and allylic alkylation

As summarized in paragraph 7.1, the substrate scope for ACA and AAA with Grignard reagents is extensive.[1] In spite of that, there are ample opportunities to extend the scope to other substrate classes which can be explored for their chemo-, regio- and stereoselective transformation using Grignard reagents (Figure 7.2). Especially, α- or (double) β- substituted ACA substrates,[v] ACA substrates with several other electron withdrawing groups (see paragraph 1.9), as well as, γ-N-substituted or β-substituted AAA substrates might be interesting.

Although not many natural products are known bearing a linear quaternary all-carbon center and a β-acyl moiety, the linear β-disubstituted substrates are both interesting from a fundamental point of view and as chiral building block. To identify a catalyst which can either distinguish between two alkyl chains or can asymmetrically transform β-substituted substrates based only on the olefin geometry (Figure 7.3) is a tremendous challenge. One of the best substrate to develop this chemistry is an α,β-unsaturated ester with stereodivergent β-substitution (for example alkyl vs. aryl).

Figure 7.2. *Potential substrates for ACA and AAA.*

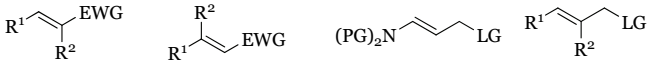
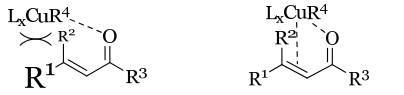


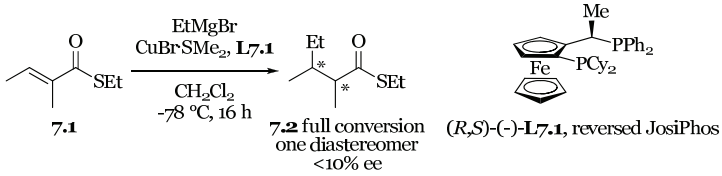
Figure 7.3. *Hypothetical intermediates for enantiodiscrimination of linear β-disubstituted substrates.*



[v] (Double) γ-substituted AAA substrates are less suited for initial studies since the competition of the S_N2 reaction will be substantial.

α-Substituted esters and ketones are abundant in natural products (see also chapter 5) and a plethora of chiral α-carbon- and oxygen-substituted ACA-products are potential building blocks for natural product synthesis. Recent results[vi] have shown that 1,4-addition of EtMgBr to *E*-S-ethyl 2-methylbut-2-enethioate using reversed JosiPhos as ligand gives the ACA product in good yield but low enantioselectivity (Scheme 7.1).

Scheme 7.1. *ACA with an α-substituted substrate using reversed JosiPhos as ligand.*



7.1 **7.2** full conversion one diastereomer <10% ee (*R,S*)-(-)-**L7.1**, reversed JosiPhos

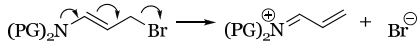
Monodentate N-heterocyclic carbene ligands have shown to be the preferred ligands to deal with steric bulk close to a reactive site. For both α- or (double) β- substituted ACA substrates the use of N-heterocyclic carbene ligands and phosphoramidite ligands should be explored.

As described in paragraph 1.10, using asymmetric conjugate reduction chiral β-substituted lactones, lactams, nitriles, nitroalkenes and aromatic heterocycles have been synthesized. Each of these products are interesting multifunctional building blocks and formation of these products via ACA would have the advantage that by the introduction of an alkyl group from the Grignard reagent at the β-position both β-substituents can be modularly chosen.[vii]

Synthesis of heteroatom building blocks is an extremely useful application of AAA.[2i,3] Especially the synthesis of optically active alcohols via AAA with Grignard reagents[4] has been an important breakthrough. The synthesis of chiral allylic amines is an alternative target for the heteroatom-AAA.

However, synthesis of the required γ-N-substituted AAA-substrates (Figure 7.2), the enamines, is not straightforward. In the last year a couple of papers[18] have reported novel and mild routes to enamines which could be explored for the preparation of γ-N-substituted AAA substrates. Furthermore, the intrinsic stability of 3-bromoenamines is not high (Scheme 7.2). The increased nucleophilicity of the nitrogen atom, compared to the oxygen atom, might allow conjugate elimination of bromide to give an enamine. A third and final problem is possible coordination of nitrogen to copper which has shown to give problems and requires further studies. To develop the *h*AAA to γ-N-substituted AAA substrates 3-bromoalkene amines double acylated on the nitrogen atom might be explored.

Scheme 7.2. *Possible pathway for conjugate elimination of the bromide from 3-bromo enamines.*

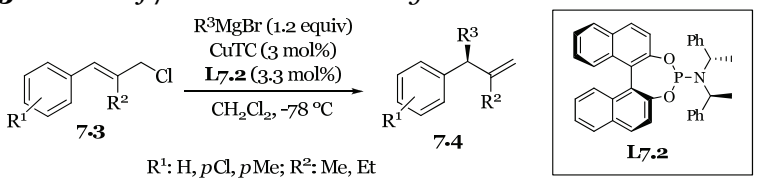


[vi] Unpublished results.

[vii] While for asymmetric conjugate reduction frequently new substrates should be prepared.

Although β-substituted cinnamyl chlorides (Scheme 7.3) have been regio- and stereoselectively transformed to give S_N2'-products,[19] aliphatic allylic substrates give a low S_N2:S_N2'- ratio.[4] Especially selective transformation of these aliphatic allylic substrates would give highly desirable multifunctional building blocks. As before the use of N-heterocyclic carbene ligands and phosphoramidite ligands should be explored.

Scheme 7.3. *The use of β-substituted cinnamyl chlorides in AAA.*



R¹: H, *p*Cl, *p*Me; R²: Me, Et
R³: Et, pentyl, homoallyl, 4-pentenyl
yield: 83-99%; γ:α= 83:7 to 92:8; ee: 92-98%
7 examples

7.4 Expanding the Grignard reagent scope for asymmetric conjugate addition and allylic alkylation

Similar to the substrate scope, the Grignard reagents scope for ACA and AAA is extensive and comprises all non-functionalized aliphatic Grignard reagents.[1] With respect to functionalized Grignard reagents, frequently the homoallyl and ethylphenyl magnesium bromides are known to give good yields, regio- and stereoselectivity for most tested substrates.[1] Although it is to be expected that the scope for functionalized Grignard reagents is more extensive, this has not been reported. Developing the ACA and AAA with functionalized Grignard reagents, including aliphatic phenyl-substituted, aliphatic terminal and internal alkene-substituted, aliphatic internal[viii] alkyne-substituted, aliphatic protected hydroxy-substituted[1] and aliphatic protected Si-substituted[20] Grignard reagents would further extend the scope of the asymmetric Cu-catalyzed chemistry.

Although recently AAA with aryl Grignard reagents has been achieved,[6] AAA and ACA of most sp^2- and sp-hybridized Grignard reagents, as well as, benzylic and allylic Grignard reagents has not yet led to satisfactory results in view of regio- and enantioselectivity. Understanding why the selectivity of ACA and AAA using sp^2- and sp-hybridized Grignard reagents is so low might be key for the development of an efficient catalytic system. Multiple hypotheses can be proposed to explain the low regio- and enantioselectivities for these Grignard reagents.

First of all, the sp^2- and sp-hybridized Grignard reagents have different steric properties compared to each other and compared to sp^3-hybridized Grignard reagents. The more bulky aryl sp^2-hybridized and less sterically encumbered sp-hybridized Grignard reagents might necessitate other chiral ligands. Furthermore, the intrinsic low reactivity of aryl Grignard reagents compared to alkyl Grignard reagents can account for changes in the mechanism. Finally, the possibility

[viii] For terminal alkynes a competing reaction might be deprotonation of the alkyne by the Grignard reagent.

of π-π stacking of the aryl and olefinic Grignard reagents might give two different phenomena. First of all, the aggregation of the Grignard reagent in solution, as well as the reactivity of these aggregates, may be quite different for aryl and olefinic Grignard reagents. To investigate the aggregation behavior, the influence of concentration on the result of the catalytic reaction should be studied. And secondly, π-π stacking with the aryl and olefinic Grignard reagents might change the coordination of the activated Cu-ligand system allowing a variety of other transition states.[ix]

In my opinion there are two possible ways to obtain more insight in ACA and AAA using sp^2- and sp-hybridized Grignard reagents. First of all, a screening of especially BINAP, phosphoramidite and N-heterocyclic carbene ligands for ACA and AAA might give additional leads. Furthermore, to better understand the reactivity of these Grignard reagents, an in-depth investigation of the properties of the sp^2- and sp-hybridized Grignard reagents is required.

As model system to explore this chemistry, linear aliphatic α,β-unsaturated esters can be used. These substrates have a low reactivity, which would hamper competing non-enantioselective 1,4-additions (leading to low ee), as well as 1,2-additions and thus give more reliable results from screenings. However, one of the main goals for this chemistry should be the transfer of the aryl group of the Grignard reagents to linear aryl-substituted α,β-unsaturated esters providing access to valuable double aryl-substituted tertiary C-centers which are important intermediates for pharmaceuticals.

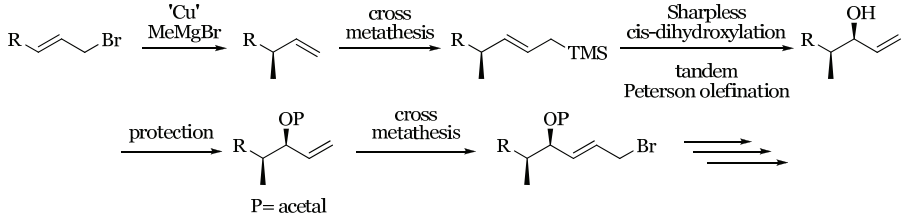
7.5 Elaboration of asymmetric conjugate addition and allylic alkylation products

Effective methods to perform catalyzed ACA and AAA using Grignard reagents[1] have become available only recently. Hence, it is unsurprising that they have not yet seen widespread application in total synthesis. However, most ACA and AAA products are valuable chiral multifunctional building blocks. Especially the thioester products of the ACA can be transformed either into a ketone using a Gilman reagent,[21] or can be reduced selectively to the aldehyde[22] and further elaborated using a Wittig or Horner-Wadsworth-Emmons olefination.[22] Finally, the thioester ACA products can be reduced to the corresponding alcohol.[23] The terminal olefin products of AAA have been shown to allow an extensive number of transformations without major loss of stereochemical integrity. Either hydroboration-oxidation,[2i] Wacker oxidation,[2i] $NaIO_4$-oxidation,[2i] ozonolysis-reduction,[2i] cross metathesis[3] (see chapter 5), diimide reduction[3] (see chapter 5), Sharpless cis-dihydroxylation[3] (see chapter 5) or iodolactonization[3] (see chapter 5) have all provided the corresponding hydroxyl-,[2i,3] dihydroxy-,[3] carboxylic acid-,[2i] ester-[2i] and ketone-containing products,[2i] as well as olefinic and[3] aliphatic[3] products and lactones.[3] With their synthetic versatility in the future the building blocks obtained via AAA and ACA will undoubtedly be used for multiple natural product syntheses.

[ix] The strength of the formed Cu-carbon bond might also be responsible for the observed selectivities, especially for the sp-hybridized Grignard reagents. See: M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 4697-4706.

The ACA has been used extensively for the iterative preparation of the abundant deoxypropionate units in nature.[22] Another warranted target for iterative synthesis are propionate units. A combination of AAA employing MeMgBr,[2h,i] cross metathesis,[24] tandem Sharpless asymmetric cis-dihydroxylation-Peterson olefination[25] and, after selective protection,[x] another cross metathesis[3] might allow the iterative construction of propionate units (see Scheme 7.4).

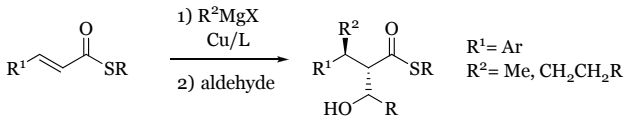
Scheme 7.4. *Iterative synthesis of propionate units.*



7.6 Tandem asymmetric conjugate addition-enolate trapping reactions

One of the most attractive aspects of the ACA of Grignard reagents is the possibility to trap the formed enolates with a variety of electrophiles. Using these tandem transformations, in principle, two novel stereogenic centers can be introduced in a single pot procedure. The current scope of the ACA tandem reactions,[26,27] using Grignard reagent for ACA, include substrate-controlled ACA-intermolecular aldol reactions for exclusively acyclic[28] substrates (Scheme 7.5). Using zinc reagents, ACA-aldol, as well as ACA-allylic alkylation and ACA-substitution reactions on cyclic and acyclic (exclusively intramolecular trappings) substrates have been reported.

Scheme 7.5. *Current scope of tandem ACA of Grignard reagents-enolate trapping reactions.*

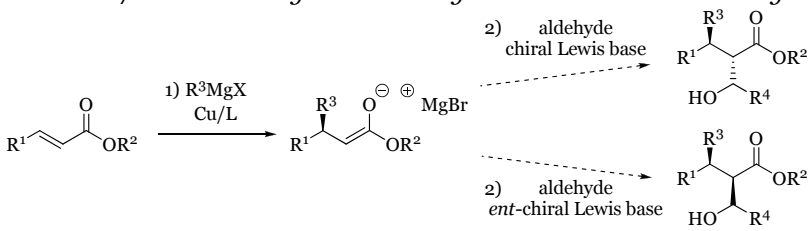


[x] Recent results by Dr. Martin Fañanás-Mastral have shown that the protective group should be forced away in space from the reactive center using an acetal, protecting both the hydroxy functionality adjacent to the reactive center and a hydroxy functionality farther away from the allylic system, to allow regio- and enantioselective AAA. This requirement will necessitate the development of a specific protection group strategy.

For the cyclic systems the limited conformational freedom of the enolate in the transition state allows high diastereoselectivity of the trapping reactions. For the intramolecular trapping reactions the limited conformational freedom in the cyclic transition state causes the observed high diastereoselectivity (see also chapter 6). Finally, for the intermolecular trapping of enolates, resulting from ACA on acyclic substrates, the high diastereoselectivity of the trapping reaction is induced by the difference in steric bulk of the substituents on the β-position, i.e. ACA-enolate intermediate is β-Ph and β-aliphatic substituted.

Until now, the full potential of ACA-enolate trapping transformations has not been exploited. All known methodologies rely on the intrinsic diastereoselection induced by the substrate to form the *anti*-products. Synthesis of the *syn*-products can be envisioned using orthogonal double catalysis. For instance catalysis of the 1,4-addition by Cu-catalysis and enolate trapping catalyzed by complementary catalysis; which would allow stereocontrol of both centers. For example the Cu-TolBINAP catalyzed ACA[9b,c,11b] could be combined with the Lewis base catalysis pioneered by Denmark and co-workers (Scheme 7.6).[29]

Scheme 7.6. *Combining ACA and asymmetric Lewis base catalysis.*



7.7 The mechanism of asymmetric conjugate addition and allylic alkylation with Grignard reagents

To understand and further develop ligand-Cu systems for ACA and AAA using Grignard reagents extensive mechanistic studies are necessary. An investigation[30] combining NMR-, electrochemistry-, kinetic- and synthetic data led to elucidation of the structures of the initial complexes and, furthermore, a general scheme for the catalytic cycle of the ACA. However, a few conclusions of this investigation still seem preliminary and further research is required.

A first topic for studies is the nature of the Grignard reagent in solution. Several reviews[31] state that the nature of the Grignard reagent (and in particular the Schlenk equilibrium) is dependent on solvent, concentration and temperature (see paragraph 1.5). However, the majority of the research was devoted to the study of the nature of Grignard reagents in THF or Et_2O.[xi] No studies are known on the constitution of Grignard reagents in *t*BuOMe, CH_2Cl_2 or 2-MeTHF and these are the solvents employed in catalysis. Investigation of the Schlenk equilibrium in these solvents might give further insight in the constitution of the Grignard reagent. Furthermore, aggregation of Grignard reagents in solution is concentration

[xi] Also toluene has been studied.

dependent and this aggregation is important for the reactivity of the Grignard reagent. Unfortunately, no studies have been performed on the concentration dependency of either ACA or AAA. Finally, details on the temperature dependency of the Schlenk equilibrium are not widely studied.[xii] As example, a (quantitative or qualitative) description of the nature of different Grignard reagents at varying temperatures has not been reported. One might expect that the Grignard reagents exhibit different aggregation at different temperatures, since the properties of the solvent (especially viscosity) change with temperature. To explain why the low temperatures are necessary for efficient catalysis it might be wise to further investigate the temperature dependency on the constitution of Grignard reagents. Furthermore, study of complexes of Grignard reagents with Cu-sources at low temperatures are needed to elucidate the influence of copper reagents on the Schlenk equilibrium.

A further topic for investigation is the development of a stereochemical model for the reaction. The current model[30] is highly preliminary and detailed insight in the reaction, especially on the mechanism, the stereochemical parameters and the actual catalyst complex(es) is needed to give an improved model.

A final topic for research is to elucidate the specific similarities and differences between the Cu-catalyzed ACA to esters, thioesters and ketones, the ACA to sulfones, the 1,6-ACA (see chapter 3), the AAA and the conjugate reduction. Possibly these reactions share some analogous intermediates since similar trends in ligands and solvents can lead to the conclusion that those reactions are closely related.

To gain more insight in the mechanism of ACA and AAA special attention should be paid to the constitution of the Grignard reagent, the kinetics of the catalytic reactions and the concentration dependency of ACA and AAA. The Cu-TolBINAP based catalytic system is worth special attention. Both the NMR-spectroscopic properties of the catalyst and the reaction conditions are well suited for mechanistic studies. The NMR signals of the catalyst are mainly concentrated in the aromatic region while NMR signals of the substrate and the Grignard reagent are located upfield. Furthermore, the temperature (-40 °C or -20 °C) at which the reaction is performed might allow the reaction to be followed by NMR spectroscopy at lower temperatures.

7.8 Conclusions

In summary, in the last decade the development of effective ACA and AAA with Grignard reagents has opened up many possibilities for the synthesis of chiral multifunctional building blocks. However, the full potential of these reactions has not been reached and several hurdles have to be overcome before the ACA and AAA with Grignard reagents will be viable alternatives for asymmetric hydrogenation in industry.

[xii] Investigation of this topic has been impeded by difficulties of analysis. I.e. the equilibria at higher temperatures have been difficult to observe because they are fast on NMR-time scale. Furthermore, only recently Raman spectroscopy and DOSY-NMR spectroscopy have been developed and will be excellent tool for this kind of investigation.

Although the work described in these thesis has added two additional substrate classes to ACA (see chapter 2 and 6) and AAA (see chapter 5), more alternative substrates can be explored for selective ACA and AAA. Furthermore, by developing ACA and AAA with functionalized sp^3-hybridized, sp^2- and sp-hybridized Grignard the scope of this chemistry can be further expanded.

Multiple methods for the elaboration of ACA and AAA product are available and the research described in this thesis (see chapter 4 and 5) has further expanded these possibilities. Furthermore, tandem reactions, selectively transforming the intermediate magnesium enolates into products with two or more stereogenic centers, are just one of the many possibilities of the ACA with Grignard reagents. The synthesis of *trans* 1,2-disubstituted cyclopropanes by tandem ACA with Grignard reagents-intramolecular enolate trapping (see chapter 6) is a valuable example of this kind of transformation. However, the full scope of these transformations is still limited and can be further developed.

Finally, the first step has been made to disclose the mechanism of 1,4- and 1,6-ACA (see chapter 3). Additional research in the coming years will hopefully shed more light on the mechanism and will allow further rational exploration of the many synthetic possibilities of ACA and AAA with Grignard reagents.

7.9 Acknowledgement

Prof. Dr. J. G. de Vries is acknowledged for fruitful discussions concerning the potential use of ACA and AAA with Grignard reagents in industry described in paragraph 7.2.

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English Summary

The word “chemistry” originates[i] either from the word “khēmia” meaning “transmutation of earth” in ancient Egyptian, or from the Greek word “χημεία” (khēmeia) translated as “cast together” or “pour together”, or alternatively from “کیمیای” (kimiya), an old Persian word for either “gold” or “transformation of elements”. Chemistry is the branch of science concerned with substances of which matter is composed, the investigation of their properties and reactions, and the use of such reactions to form new substances.[ii]

Mainly chemistry studies matter at the molecular and atomic scale. A molecule consists of small basic elements called atoms.[iii] Atoms vary in size from roughly 30 to 200 picometer. Molecules can exist of for instance a three atoms (an example is a single molecule of water, Figure S1, consisting of a central oxygen atom which is connected to two hydrogen atoms by two single bonds) up to an, in principle, unlimited amount of atoms (an example are plastics, they consists of thousands of single atoms connected to a long chain).

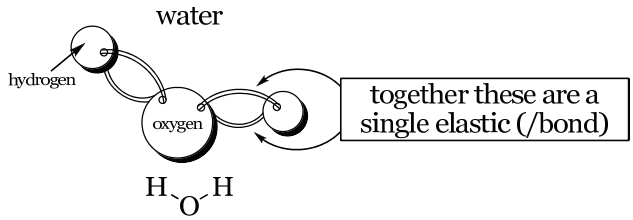

Figure S1. *Depiction of a (simplified!) beads and elastic model of a molecule of water (top) and the chemical notation of a molecule of water (bottom).*

Two molecules can interact with each other by either attracting or repelling one another or they can change the shape of the molecules by attracting parts of a molecule and repelling other parts. Of most interest to chemists however, is that they can react which one another (Figure S2, next page). The latter means that some of the bonds/elastics in the molecules are broken and new bonds are formed, resulting in one, two or even more novel molecules.

The Dutch word for “chemistry” is “scheikunde”, which literally means “science of separation”. The Dutch name for chemistry was chosen since the reaction of two molecules most often gives a mixture of products that need to be separated in order to obtain a pure product from a reaction (a pure product means a sample containing only one type of molecule). Although in the early days of chemistry “scheikunde” was a fitting translation, nowadays chemical research is especially directed at developing new methods to obtain selectively (ideally without any unwanted side-products and thus no need for separation) a desired product. Developing new selective chemical transformations is called method development and is the main topic of this thesis.

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[i] http://en.wikipedia.org/wiki/Chemistry_(etymology)

ii http://www.oxforddictionaries.com/view/entry/m_en_gb0141160#m_en_gb0141160

[iii] Atoms themselves consist of even smaller particles. However the study of those smaller particles is part of physics.

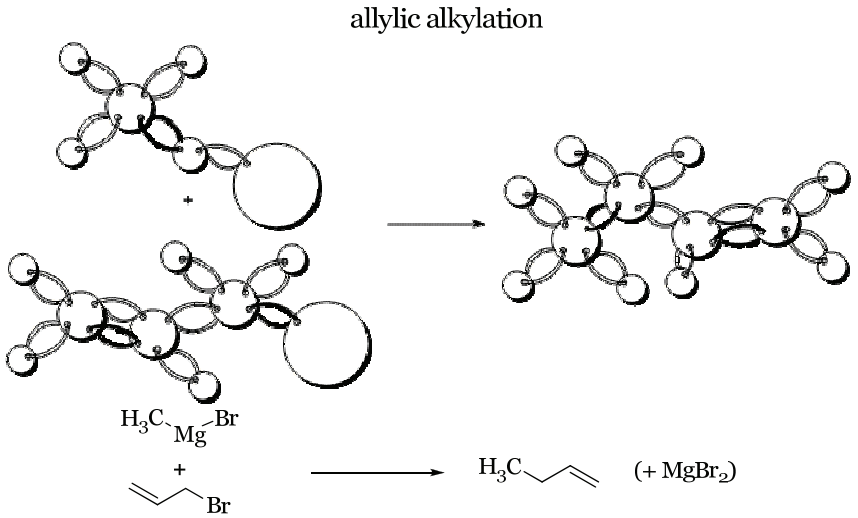


Figure S2. *Depiction of a chemical reaction (allylic alkylation) with the (simplified) beads and elastic model (top) and the chemical notation (bottom). In the beads and elastic model the black bonds are broken before the reaction (left side) or have been formed in the product (right side). In the chemical notation carbon-atoms are either annotated by a C or at the corners of the lines and (most hydrogen-atoms are omitted for clarity).*

Molecules exist since they are a stable combination of atoms (else they logically would fall apart into an alternative more stable combination of atoms). However, when two molecules interact with each other they might be able to form one or even more compounds with an overall more stable combination of atoms. However before they will form the new combination of atoms from their original state, energy needs to be added to form the new bonds.

The reason why molecules react with each other in a certain manner can be explained by an example. Imagine yourself standing in a maze with one of your friends at a T-junction (Figure S3a). Whatever direction you choose the two of you will have to climb a hill. Now since the hills are different in height and you do not have any clue where the exit is, the easiest choice would be to explore the lowest hill first to see if the exit is behind that hill.

A chemical reaction will proceed more or less in the same way. If two molecules interact with each other they will have to "choose" between several distinctive energy barriers[iv] (hills, Figure S3b) and they will take the pathway which 'costs' overall the least energy.[v]

When the hills are really distinctive in height the choice for the lowest hill is an easy one. However, if in the maze (or the reaction) the two lowest hills are close in height (for the reaction in energy) the two of you might decide to choose the one-to-lowest hill, instead of the lowest hill.

[iv] The energy barrier is mainly formed by electrostatic interactions (tiny magnets attracting and repelling each other).

[v] This does not mean that the reacting molecules actually always form the product 'behind' the lowest energy barrier. This is dependant on a large amount of factors, from which the enthalpy and entropy of a certain system are most important.

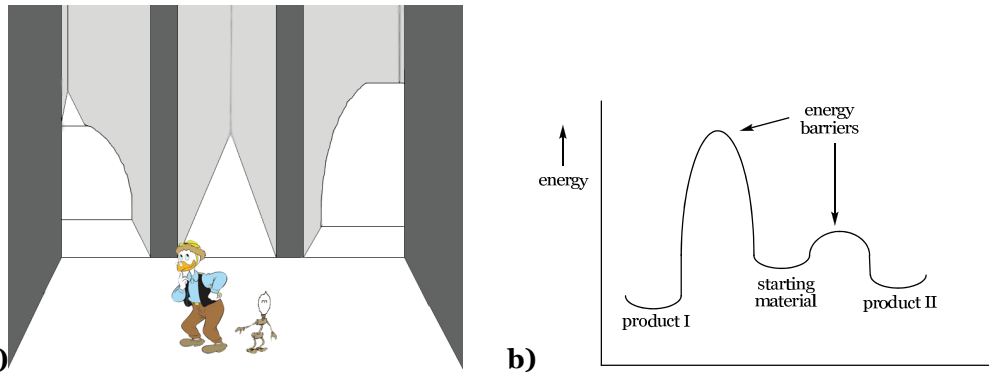


Figure S3. a) *At the crossroad of a maze (left). The two persons in the picture will take the middle entrance since there is no hill in this entrance and it will thus make them least tired.* **b)** *Energy diagram of a reaction (right). In the middle the combined energy level of the starting materials is depicted. The product of this reaction will (mainly) be product II since the energy barrier towards this product is much lower.*

Although chemists draw a chemical reaction as 1 molecule reacting with 1 other molecule, reactions typically involve multiple billions of molecules which will react in a similar fashion. Now when the two lowest energy barriers are close in height (and lead to different products) the majority of molecules will form the product "behind" the lowest energy barrier. However, a substantial part of the molecules will also react "via" the one-to-lowest energy barrier (so choose the one-to-lowest hill), giving a mixture of products.

Chemists often do not want the product which is "lying" behind the lowest energy hill, or do not want to obtain a mixture of products. In that case chemists change certain parameters to try to force the reaction to proceed more selectively. An examples of such a parameter is the solvent in which the reaction is performed and another parameter is the temperature at which the reaction is performed. In this thesis in order to develop novel methods we vary some parameters. However, mainly we use another "trick" to force reactions to proceed selectively; which is called catalysis. In catalysis an additional compound (a so-called catalyst) is added to the reaction to make a reaction more selective (or to accelerate a reaction).

Imagine that in the maze the exit (which can be compared to the desired product) actually lies behind the highest hill. What a catalyst[vi] then would do is dig a tunnel through the highest hill (energy barrier, Figure S4a, next page) and thus allowing you and your friend to reach the exit using minimal energy.

There is one more aspect of catalysis which needs to be introduced. The catalysis described in this thesis is aimed at preparing enantiopure molecules and is called either asymmetric or enantioselective catalysis. What does that mean?

Some molecules incorporate at least one stereogenic center[vii] (an atom surrounded with four different substituents) and are called chiral since an exact, non-identical mirror image of that molecule exists. Examples of chiral objects are your hands.

[vi] The catalyst can also roughly be compared to the flame which melts one end of an elastic to allow the two elastics to be melted together (without the flame [catalyst] the new bond would not be formed)

[vii] These molecules should not possess an internal mirrorplane.

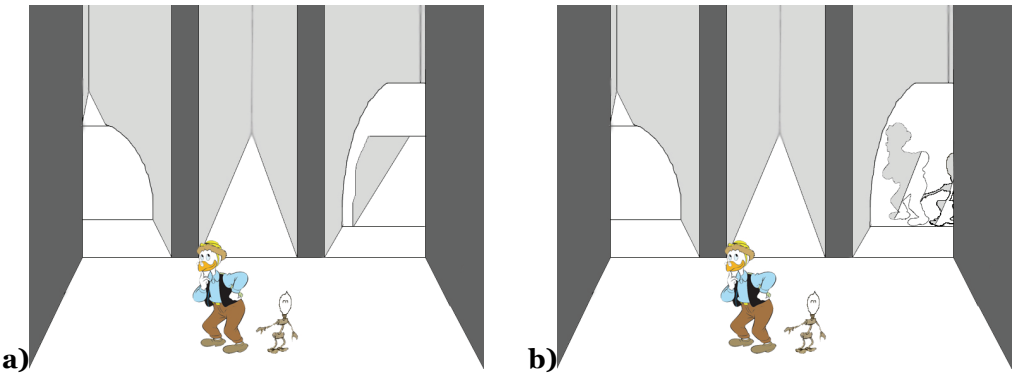


Figure S4. a) *Again at the crossroad of a maze. The two persons in the picture will take either the middle entrance or the right entrance since there is no hill in the middle entrance and at the right entrance the "catalyst" has dug a hole through the hill.*
b) *Once more at the crossroad of a maze. The tunnel made in the right hill can only be passed if the left person walks on the left and the right person walks on the right.*

When you put your left hand in front of the mirror you will see your right hand in the mirror. When one of the two mirror images of a molecule is selectively made, this is called asymmetric or enantioselective synthesis. Now, when catalysis is used for asymmetric synthesis it is called asymmetric catalysis. When we go back to the example of the maze, asymmetric catalysis (again simplified!) corresponds to creating a defined hole in the hill through which you and a friend can only walk when you are walking on the left side and your friend is walking on the right side, and not when you are walking on the right side (Figure S4b).

Why would you want to do asymmetric catalysis? The most important regulatory systems in our bodies are formed by large molecules; called proteins. Proteins consist of a repetition of, typically several hundreds, of smaller chiral subunits, amino acids. For a yet unknown reason the proteins in our bodies are constructed of (almost exclusively) one enantiomer of the amino acids. Although two enantiomers of a molecule share most of their physical properties, when they interact with one or the other of the two enantiomers of another molecule different interactions are observed. To allow a compound to act like a drug and thus interact in a beneficial way with our bodies a single enantiomer of a compound is often required (since it will need to interact with one enantiomer of the amino acids). That is why we do asymmetric catalysis.

The research described in this thesis is primarily aimed at exploring challenging substrates for which multiple selectivity issues arise. Thus, using asymmetric catalysis to force reactions for which a couple of low hills exist to give only one enantiomer of the desired product.

In Chapter 1 an introduction on asymmetric catalysis and, in particular, Cu-catalyzed asymmetric conjugate addition of, and asymmetric allylic alkylation using Grignard reagents is given. The two reactions using Grignard reagents are carbon-carbon bond forming reactions for which the initial protocols were available before the research for this thesis had started. These reactions are thus the basis for the research described in this thesis.

The first part of this thesis deals with multiple unsaturated Michael acceptors as substrates for asymmetric conjugate addition with Grignard reagents. In chapter 2

the first method for enantioselective 1,6-addition primarily dictated by the catalyst is described. For this asymmetric 1,6-addition to proceed selectively further regioselectivity issues, compared to asymmetric 1,4-addition, had to be solved. After optimization, a variety of alkyl Grignard reagents could be added in a 1,6-fashion to several alkyl-substituted α,β,γ,δ-bisunsaturated esters in good yield (up to 88%) and excellent regio- (up to 99:1) and enantioselectivity (up to 97% ee).

In chapter 3, initial and primarily structural studies towards a mechanism for extended conjugate additions are reported. In this chapter the way the hole in the "hill" (or for the reaction the energy barrier) is made is investigated. From the results of these studies a preliminary model for extended conjugate additions is proposed. Furthermore, it is concluded that the C4-olefin is probably involved in the enantiodiscriminating step of the mechanism. Further studies are needed to validate both conclusions.

In chapter 4 the synthetic application of the asymmetric 1,6-addition for the construction of deoxypropionate units is explored. These deoxypropionates are important subunits of a variety of natural products. The novel iterative method comprises an extended Horner-Wadsworth-Emmons reaction with a novel α,β-unsaturated thioester reagent, asymmetric Cu-catalyzed 1,6-conjugate addition, base catalyzed olefin isomerization and Cu-catalyzed enantioselective 1,4-conjugate addition. It is concluded that the method described in this chapter can compete with existing methods for the iterative construction of the deoxypropionate subunits.

In the second part of this thesis, 4-halocrotonates are explored as substrates. These substrates possess all structural features to either allow allylic alkylation or conjugate addition. In chapter 5 the enantioselective allylic alkylation of benzyl 4-bromocrotonate with MeMgBr leads to highly warranted α-Me substituted esters. To illustrate the versatility of these products, they have been elaborated to multifunctional building blocks with a single or with multiple stereogenic centers. However, developing a general method for the selective synthesis of α-alkyl substituted esters via allylic alkylation (using other, more reactive, alkyl Grignard reagents) was unsuccessful so far.

In chapter 6 the enantioselective conjugate addition of Grignard reagents to 4-halocrotonates is described. Cu-TolBINAP catalyzed conjugate addition of Grignard reagents to 4-chloro α,β-unsaturated esters, thioesters and ketones leads to 4-chloro-3-alkylsubstituted thioesters and ketones in up to 84% yield and up to 96% ee. Furthermore, tandem conjugate addition-enolate trapping yields *trans* 1-alkyl-2-substituted cyclopropanes in up to 92% yield and up to 98% ee. The versatility of this reaction is illustrated by the formal syntheses of cascarillic acid and grenadamide. Furthermore, a synthetic route to majusculoic acid as well as an approach for the synthesis of tri-1,2,3-substituted cyclopropanes are proposed.

Finally, in chapter 7 a summary of the current status of the field of asymmetric conjugate addition and allylic alkylation using Grignard reagents is given and future prospects for this field are discussed. Currently, although the conjugate addition and allylic alkylation reactions are perfectly suited to be used in academic research (which does not have to be extremely cost-efficient since most academic research is performed at small scale and is primarily aimed at understanding the reactions or the specific physical properties of a molecule), for industrial purposes (large scale manufacturing of compounds) further research is needed to make allylic alkylation and conjugate addition with Grignard reagents more cost-efficient. In particular, research should be directed towards allowing the reactions to be performed at

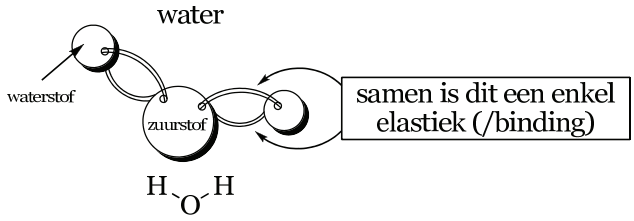
higher temperatures (0 °C to ambient temperature), while retaining good selectivity and yield.

In summary, several novel methodologies have been developed for asymmetric formation of C-C bonds. These novel methodologies are extremely well suited for use in the synthesis of important chiral molecules and provide an excellent basis for further method development or natural product synthesis. Furthermore, a start has been made to gain more insight in the mechanisms of these reactions.

Nederlandse Samenvatting

Het engelse woord “chemistry” kan afstammen[i] van woorden uit drie verschillende uitgestorven talen. Of het komt uit het oude egyptisch waar het woord “khēmia” “transformatie van aarde” betekent, óf van het oud griekse woord “χημεία” (khēmeia) dat wordt vertaald door “samengieten” of “samenstorten”, óf uit het oude perzisch waar “کیمیای” (kimiya) twee betekenissen heeft, namelijk “goud” of ”transformatie van elementen”. Waar het woord ook van afstamt “chemistry” is de wetenschap die materie op de atomaire tot moleculaire schaal bestudeert; en dan vooral de verschillende interacties die moleculen met elkaar kunnen hebben.

Maar wat is eigenlijk een molecuul? Een molecuul bestaat uit kleine basiseenheden die atomen genoemd worden.[ii] Atomen varieren in grootte van 30 tot 200 picometer (erg klein dus). Deze grootte betekent dat in de ruimte tussen je gespreide duim en wijsvinger ongeveer 1 miljard atomen passen in een enkele rij. Als je atomen vereenvoudigt kun je ze voorstellen als kleine kralen. Moleculen zijn dan opgebouwd uit verscheidene atomen die zijn verbonden met (één of meerdere) chemische bindingen die (alweer vereenvoudigd!) kunnen worden voorgesteld als elastiek. Moleculen kunnen bestaan uit maar een paar atomen (een voorbeeld is water, Figuur S1, dat bestaat uit een centraal zuurstof atoom dat verbonden is met twee waterstof atomen, elk verbonden met een enkele binding) tot aan een heel groot aantal atomen (bijvoorbeeld plastics, deze bestaan uit ketens van duizenden atomen).



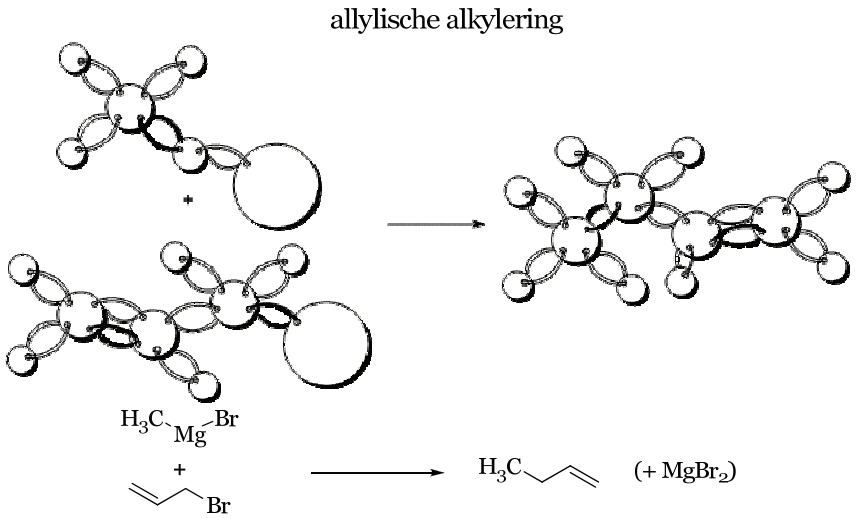
Figuur S1. *Een molecuul water weergegeven als kralen en elastieken (bovenaan) en zoals scheikundigen dit molecuul weergeven (onderaan).*

Twee moleculen kunnen interactie hebben met elkaar door een ander molecuul af te stoten, óf juist aan te trekken. Verder kunnen moleculen elkaar van vorm laten veranderen (zoals je je kunt voorstellen: kralen verbonden met elastieken zijn erg flexibel) door een deel van een ander molecuul aan te trekken en een ander deel af te stoten. Tenslotte kunnen moleculen ook met elkaar reageren (Figuur S2, volgende pagina). Dit laatste betekent dat sommige bindingen/elastieken binnen een molecuul worden verbroken en andere bindingen worden gevormd, wat resulteert in één, twee of zelfs meer nieuwe moleculen.

In het Nederlands wordt “chemistry” vertaald als “scheikunde”, de wetenschap van het scheiden. De Nederlandse vertaling voor “chemistry” is zo gekozen omdat de reactie van twee moleculen vaak een mengsel van producten geeft. Deze producten moeten na de reactie gescheiden worden om een zuiver product te geven (een zuiver product betekent een hoeveelheid van precies dezelfde moleculen). Vroeger was het nederlandse “scheikunde” een goede vertaling van “chemistry”. Tegenwoordig is chemisch onderzoek er vooral op gericht om methodes te

[i] http://en.wikipedia.org/wiki/Chemistry_(etymology)

[ii] Atomen bestaan zelf weer uit kleinere basiseenheden. De studie van deze subatomaire deeltjes is deel van de natuurkunde.



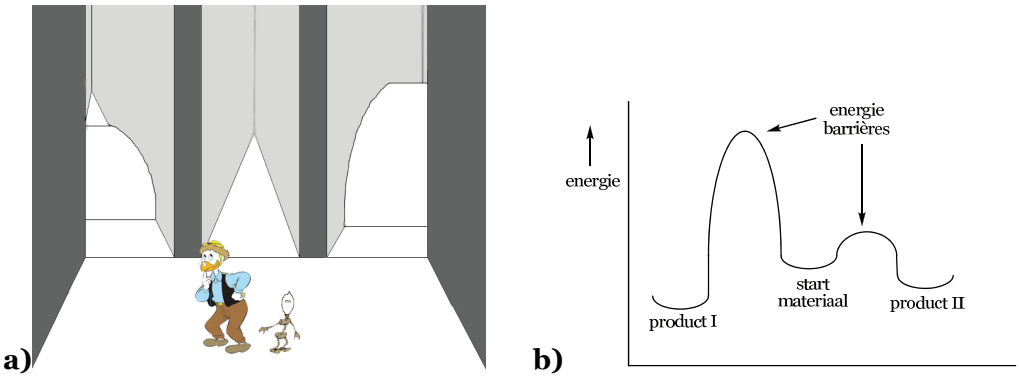
Figuur S2. Weergave van een chemische reactie *(allylische alkylering) met kralen en elastieken (bovenaan) en in chemische notatie (onderaan). De zwart-gekleurde bindingen worden in het kralen-en-elastiek model verbroken in de reactie (links van de pijl) of gevormd tijdens de reactie (rechts van de pijl). In de chemische notatie worden de koolstof atomen weergegeven als een C óf als de hoekpunten van de lijnen (bijna alle H (waterstof) atomen worden weggelaten voor de overzichtelijkheid).*

ontwikkelen om selectief (idealiter zonder bij-producten te vormen en dus zonder scheiding nodig te hebben) een product te vormen (een nieuw molecuul). Het ontwikkelen van nieuwe selectieve chemische methodes wordt methodeontwikkeling genoemd en is het hoofdonderwerp van dit proefschrift.

Moleculen kunnen bestaan omdat ze een stabiele combinatie van atomen zijn (anders zouden ze uiteenvallen tot een andere, wel stabiele combinatie van atomen). Maar als moleculen met elkaar een interactie hebben kunnen ze soms één of meer nieuwe stoffen (een verzameling moleculen) vormen met een, in totaal, meer stabiele combinatie van atomen. Maar voordat ze vanuit hun uitgangsstoffen deze nieuwe combinatie van atomen vormen, is er energie nodig om bindingen te verbreken en nieuwe bindingen te vormen. Dit kan je vereenvoudige voorstellen als het aan elkaar smelten van de uiteinden van de elastieken om twee kralen te verbinden.

Waarom moleculen met elkaar reageren op een bepaalde manier kan het beste uitgelegd worden met een voorbeeld. Stel je voor dat jij in een doolhof bij een kruispunt staat met een van je vrienden, waarbij jullie in drie richtingen verder kunnen gaan (Figuur S3a). Welke richting jullie ook op gaan er moet een heuveltje beklommen worden. Aangezien de heuvels verschillende hoogtes hebben en jullie geen idee hebben waar de uitgang is, is de meest logische keus om als eerste over de laagste heuvel te gaan om te onderzoeken of achter deze heuvel de uitgang van het doolhof ligt.

Een chemische reactie zal ongeveer op dezelfde manier plaatsvinden. Als twee moleculen een interactie hebben met elkaar, moeten ze “kiezen” tussen twee verschillende energie barrières (heuvels, Figuur S3b) en zullen ze de laagste



Figuur S3. a) *Op het kruispunt van een doolhof (links). De twee personen in het figuur zullen de middelste route nemen aangezien dit hun de minste inspanning kost.* **b)** *Energie diagram van een reactie (rechts). In het midden is het (opgetelde) energie niveau van de uitgangsstoffen weergegeven. Het product van de reactie zal (vooral) product II zijn aangezien de energie barrière om dit product te vormen veel lager is.*

barrrière nemen.[iii]

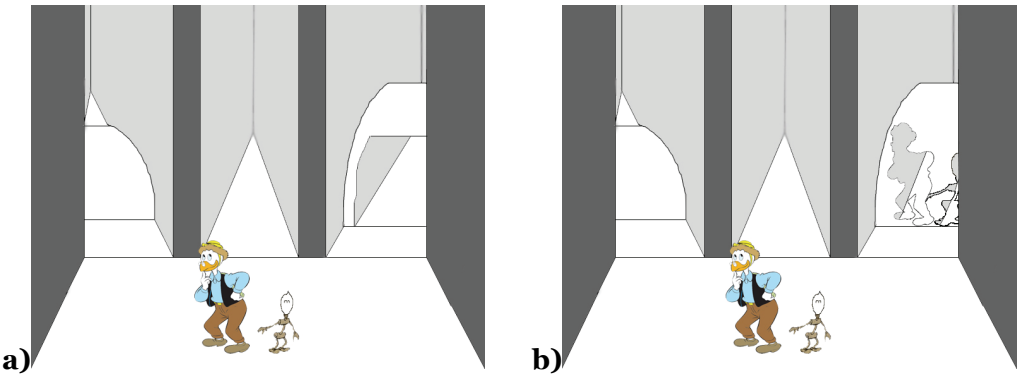
Als de heuvels erg verschillend zijn in hoogte is de keus makkelijk. Maar als de twee laagste heuvels in het doolhof (of de reactie) ongeveer gelijk in hoogte (voor de reactie ongeveer gelijk in energie) zijn, dan kunnen jullie in het doolhof ook kiezen om over de een-na-laagste heuvel te gaan.

Ondanks dat scheikundigen een reactie tekenen als een reactie van één molecuul met één ander molecuul, reageren in één reactie in werkelijkheid enkele miljarden moleculen met elkaar. Als nu de twee laagste energie barrières weinig verschillen in hoogte (en ook nog eens leiden tot verschillende producten), zullen de meeste moleculen het product “achter” de laagste energie barriere vormen. Maar een ander deel van de moleculen zal “via” de op één-na-laagste energie barriere reageren naar een ander product. Daardoor zal de reactie een mengsel van verschillende producten geven.

Soms willen chemici juist niet het product krijgen wat achter de laagste energie barriere “ligt”, verder willen ze meestal niet een mengsel van producten krijgen. In deze gevallen zullen chemici verschillende “parameters” veranderen om de reactie selectiever te laten verlopen. Een voorbeeld van zo’n “parameter” is het oplosmiddel waarin de reactie wordt gedaan (een hoeveelheid moleculen van een stof die niet mee reageert met de moleculen die in de reactie met elkaar moeten reageren). Een ander voorbeeld van zo’n parameter is de temperatuur waarbij de reactie wordt uitgevoerd.

Om in dit proefschrift nieuwe reacties te ontwikkelen varieren we een aantal parameters. Maar vooral gebruiken we een andere “truuk” om de reacties te dwingen selectiever te verlopen (dus om meer van het gewenste product te vormen): namelijk katalyse. Bij katalyse wordt een extra stof (een zogenoemde katalysator) aan de reactie toegevoegd om een reactie selectiever te maken (of een bepaalde reactie te versnellen)

[iii] Dit betekent niet dat noodzakelijk ook het product achter de laagste energiebarriere gevormd wordt. Dit is afhankelijk van een groot aantal factoren, waarvan de enthalpie en de entropie van een reactie de belangrijksten zijn.



Figuur S4. a) *Alweer op het kruispunt van een doolhof. De twee personen zullen of de middelste of de rechter ingang nemen aangezien er geen heuvel ligt in de middelste ingang en aangezien bij de rechteringang de "katalysator" een tunnel door de heuvel heeft gegraven.* **b)** *Nogmaals op het kruispunt van een doolhof. Door de tunnel in de rechteringang passen de twee personen alleen als de linker persoon aan de linkerkant loopt en de rechterpersoon aan de rechterkant loopt.*

Stel je voor dat in het doolhof de uitgang (die kan worden vergeleken met het gewenste product van een reactie) achter de hoogste heuvel blijkt te liggen. Wat een katalysator[iv] dan zal doen is een tunnel "graven" door deze heuvel (energie barriere, Figuur S4a) om jou en je vriend de uitgang van het doolhof te laten bereiken met de minste inspanning.

Er is één aspect van katalyse dat nog niet is geintroduceerd. De katalyse beschreven in dit proefschrift is bedoeld om enantiomeer zuivere moleculen te maken en wordt asymmetrische of enantioselectieve katalyse genoemd. Wat betekent dit?

Sommige moleculen hebben op zijn minst één stereocentrum (een atoom omringd door vier verschillende substituenten) en worden chiraal genoemd omdat er een exact spiegelbeeld van dit molecuul bestaat.[v] Een voorbeeld van chirale objecten zijn je handen. Je beide handen zijn verschillend maar wanneer je je linkerhand voor de spiegel houdt zie je een rechterhand in de spiegel. Wanneer één van deze spiegelbeelden van een molecuul selectief gemaakt wordt, wordt dit asymmetrische of enantioselectieve synthese genoemd. Als nu een katalysator wordt gebruikt voor asymmetrische synthese wordt dit asymmetrische katalyse genoemd. Als we nu terug gaan naar het voorbeeld van jou en je vriend in het doolhof dan zal asymmetrische katalyse overeenkomen met een exact (precies naar je lichaam) gevormde tunnel in een heuvel. Door deze tunnel kunnen jullie alleen lopen als jij aan de linkerkant loopt en je vriend aan de rechterkant, en niet als jij aan de rechterkant loopt (Figuur S4b).

Waarom doen we asymmetrische katalyse? Wij, mensen, bestaan uit moleculen. De belangrijkste regelsystemen in ons lichaam, denk bijvoorbeeld aan ons afweersysteem -het systeem in ons lichaam dat zorgt dat wij niet (of in ieder geval

[iv] Een katalysator kan ook ongeveer worden vergeleken met de vlam die een uiteinde van een elastiek smelt, zodat de twee uiteinden van de elastieken verbonden kunnen worden (zonder de vlam [katalysator] zal de nieuwe binding niet gevormd kunnen worden)

[v] Deze moleculen mogen geen intern spiegelvlak bezitten.

minder) ziek worden- bestaan uit grote moleculen; eiwitten genaamd. Eiwitten bestaan uit een herhaling van, normaal gesproken, enkele honderden, kleinere chirale eenheden, aminozuren. Om een nog onbekende reden zijn de eiwitten in ons lichaam bijna helemaal opgebouwd uit maar één enantiomeer (spiegelbeeld) van deze aminozuren. De twee enantiomeren van een molecuul hebben vrijwel dezelfde fysische eigenschappen (zoals smeltpunt en kookpunt). Maar de twee enantiomeren zullen verschillende interacties hebben met elk van de enantiomeren van een ander molecuul. Om nu bijvoorbeeld als een medicijn te kunnen werken, en dus een positieve interactie te hebben met ons lichaam, is het vaak nodig om één enkele enantiomeer van een molecuul te maken (aangezien dit molecuul dus met één enantiomeer van de aminozuren interactie moet hebben). Dat is waarom we asymmetrische katalyse doen.

Het onderzoek beschreven in dit proefschrift is vooral gericht op het onderzoeken van uitdagende substraten (uitgangsstoffen) waarvoor het moeilijk is één selectieve reactie te laten plaatsvinden. Dus, we willen asymmetrische katalyse gebruiken om reacties te dwingen om één enantiomer van een product te geven terwijl voor deze reacties verscheidene lage energie-paden beschikbaar zijn. Jammer genoeg is niet al het onderzoek wat we gedaan hebben in dit proefschrift zonder vaktaal uit te leggen. In de volgende alinea's volgt een samenvatting (in meer wetenschappelijke taal) wat voor dit proefschrift onderzocht is.

In hoofdstuk 1 wordt asymmetrische katalyse geintroduceerd. Het gaat daarbij vooral om koper-gekatalyseerde asymmetrische geconjugeerde additie van, en asymmetrische allylische alkylering met Grignard reagentia. Deze twee reacties zijn belangrijke reacties waarbij koolstof-koolstof bindingen worden gevormd. De eerste protocollen voor deze reacties zijn ontwikkeld nog voordat het onderzoek beschreven in dit proefschrift begon en dienen dus als basis voor de nieuwe methodologie ontwikkeld in dit proefschrift.

Hierna gaat het in het eerste deel van dit proefschrift vooral over één specifiek soort substraten; de meervoudig onverzadigde Michael acceptors. In hoofdstuk 2 wordt de eerste methode voor enantioselectieve 1,6-additie, voornamelijk gestuurd door de katalysator beschreven. Voor deze reactie is extra controle over de regioselectiviteit nodig, zeker ten opzichte van de normale conjugaat (1,4-) addities. Na optimalisatie geven verscheidene alkyl Grignard reagentia een 1,6-additie aan een aantal alkyl-gesubstitueerde α,β,γ,δ-dubbel onverzadigde esters. Deze reacties geven de 1,6-additie producten met goede opbrengst (tot 88%) en zeer goede regio- (tot 99:1) en enantioselectiviteit (tot 97% ee).

In hoofdstuk 3 worden initiele, vooral structurele studies naar het mechanisme van de 1,6-, 1,8-, 1,x-addities beschreven. In dit hoofdstuk wordt nagegaan hoe "de tunnel in de heuvel" (voor de reactie de verandering [verlaging] van de energie barriere) is gemaakt. Aan de hand van de resultaten van deze studies wordt een hypothetisch mechanistisch model voor deze addities voorgesteld. Daarnaast wordt geconcludeerd dat het C4-olefine waarschijnlijk is betrokken in de reactiestap waar de enantioselectviteit tot stand komt. Meer studies zijn nodig om deze conclusies verder te onderbouwen.

In hoofdstuk 4 wordt de toepassing van de asymmetrische 1,6-additie in de synthese van "deoxypropionaat" eenheden onderzocht. Deze "deoxypropionaten" zijn belangrijke basiseenheden in verscheidene natuurproducten. De iteratieve methode beschreven in dit hoofdstuk bestaat uit een serie opeenvolgende reacties: een "extended Horner-Wadsworth-Emmons" reactie met een nieuw onverzadigd

thioester reagens, een asymmetrische Cu-gekatalyseerde 1,6-additie, een base gekatalyseerde olefine isomerisatie en een Cu-gekatalyseerde enantioselectieve 1,4-additie. Er wordt geconcludeerd dat de iteratieve methode beschreven in dit hoofdstuk competitief is met bestaande methodes om deze basiseenheden te synthetiseren.

In het tweede deel van dit proefschrift worden de "4-halocrotonaten" gebruikt als substraten. Deze substraten beschikken over alle structurele eigenschappen om ofwel allylische alkylering, ofwel conjugaat additie mogelijk te maken, alleen niet tegelijkertijd. In hoofdstuk 5 worden door enantioselectieve allylische alkylatie met MeMgBr van benzyl 4-bromocrotonaten interessante α-Me gesubstitueerde esters gesynthetiseerd. Om te illustreren dat de producten van deze reactie breed inzetbaar en erg bruikbaar zijn worden vanuit deze gesubstitueerde esters multifunctionele chemische bouwstenen met één enkel stereocentrum of zelfs met meerdere stereocentra gesynthetiseerd. Jammer genoeg is het niet gelukt om een meer algemene methode te ontwikkelen voor de selectieve synthese van α-alkyl gesubstituteerde esters via allylische alkylering (door middel van reactie van halocrotonaten met alkyl Grignard reagentia die reactiever zijn dan MeMgBr).

In hoofdstuk 6 wordt de enantioselectieve geconjugeerde additie van Grignard reagentia aan 4-halocrotonaten beschreven. Cu-TolBINAP gekatalyseerde geconjugeerde additie van Grignard reagentia aan 4-chloro α,β-onverzadigde esters, thioesters en ketonen leidt tot 4-chloro-3-alkyl gesubstituteerde thioesters en ketonen met een opbrengst tot 84% en een enantiomere overmaat tot 96%. Verder geeft tandem geconjugeerde additie en intramoleculaire trapping van het enolaat *trans* 1-alkyl-2-gesubstituteerde cyclopropanen met een opbrengst tot 92% en een enantiomere overmaat tot 98%. De toepasbaarheid van de reactie wordt geillustreerd door de bereiding van intermediairen voor de synthese van "cascarillic acid" and "grenadamide". Verder wordt een hypothetische route voor de synthese van het natuurproduct "majusculoic acid" beschreven en wordt een route voor de synthese van 1,2,3-trigesubstituteerde cyclopropanen voorgesteld.

Tenslotte wordt in hoofdstuk 7 een samenvatting gegeven van de huidige status van het onderzoeksveld van de asymmetrisch geconjugeerde additie en de allylische alkylering met Grignard reagentia en wordt de toekomst van deze onderzoeksvelden besproken. De geconjugeerde additie en de allylische alkylering zijn op dit moment prima geschikt voor academisch onderzoek. Onderzoek aan de universiteiten is namelijk minder op kosten-efficiëntie gericht, aangezien de reacties op kleine schaal plaatsvinden, maar vooral op het begrijpen van reacties of van specifieke physische eigenschappen van één molecuul of een aantal moleculen. Deze reacties moeten voor industriele doeleinden (grote schaal productie van stoffen) nog verder ontwikkeld worden om ze meer kosten-efficiënt te maken. Vooral moet verder onderzoek gedaan worden om deze reacties te laten plaatsvinden bij hogere temperaturen (0 °C tot 20 °C) met behoud van de goede opbrengsten en selectiviteiten.

Samengevat zijn er verschillende nieuwe methoden ontwikkeld voor het asymmetrisch synthetiseren van koolstof-koolstof bindingen. Dit vormt een goede basis voor verdere ontwikkeling van nieuwe methodologie en voor de synthese van natuurproducten. Ook is er een begin gemaakt met studies om meer inzicht te krijgen in het mechanisme van de reacties die in dit proefschrift ontwikkeld zijn.

Dankwoord/Acknowledgment

It is already more than four years ago that I moved to the (even farther) north to start my PhD-research. From the moment I started in the Feringa labs, I have been glad I had made the decision to move to Groningen. In addition to the notorious diversity and quality of the chemical research and the allowed freedom in the choice of research projects, the lab also excels in the quality of the inhabitants. The wide diversity of nationalities and personal interests has made my stay in Groningen extremely pleasant and exciting.

Research to obtain a PhD cannot be done single-handedly and I have to thank a lot of people. Before I will start to mention the people in Groningen, I would like to start by thanking Jan van Maarseveen, Henk Hiemstra, Géraldine Masson and Olivier David who have taught me the principles of chemical research.

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Tim